VOLUME 8 NUMBER 4

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OCTOBER, 1929

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, Jan. 20, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in the Act of Feb. 28, 1925, authorized Jan. 27, 1926.

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ARCHIVES OF PATHOLOGY

VOLUME 8 OCTOBER, 1929 NUMBER 4

AN INTERPRETATION OF MALIGNANT GROWTH BASED ON THE CHEMISTRY OF CELL DIVISION*

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PHILADELPHIA

Proliferation of cells is the common defining characteristic of all malignant growths. It follows that the problem of malignancy centers itself primarily on the processes of cell reproduction. The question of inciting agents is secondary, since all these produce but one biologic reaction, namely, cell proliferation. Once the chain of reactions leading to increase in cell number has been set off in a receptive field, further development depends on the intrinsic biologic characteristics of the tissue in which the growth is taking place, regardless of the nature of the agent which upsets the previously existing equilibrium.

Now cell division is the expression of underlying physicochemical processes. The physical forces condition the degree of the reaction, the nature of which is determined by the type of the interreacting chemical groups and molecules. It is therefore clear that the most logical way to approach the problem is through a study of the chemical processes specific for growth by increase in cell number.

The nub of the matter rests on the knowledge of the chemical stimulus or stimuli specifically essential to cell division. This is primary. All else is secondary. The difference in H-ion concentration of the malignant cell as compared with the normal,[1] the difference in carbohydrate metabolism,[2] the difference in proteolytic activity,[3] all these, and more, are but sequelae of the heightened reproductivity of the cell.

* Submitted for publication, June 10, 1929.

* From the Research Institute of the Lankenau Hospital.

1. Millet, H.: Measurements of the p_H of Normal, Fetal, and Neoplastic Tissues by Means of the Glass Electrode, J. Biol. Chem. **78**:281, 1928. Harde, E., and Henri, P.: Sur le p_H des néoplasmes et des embryons de souris déterminé par la coloration vitale, Compt. rend. Soc. de biol. **96**:335, 1927.

2. Warburg, O.: Milchsäurgärung der Tumoren, Klin. Wchnschr. **6**:2047, 1927. Baker, S. L.; Dickens, F., and Gallimore, E. J.: The Glycolytic Action of Some Tumors and the Effect of Insulin, Brit. J. Exper. Path. **10**:19, 1929. Crabtree, H. G.: The Carbohydrate Metabolism of Certain Pathological Overgrowths, Biochem. J. **22**:1289, 1928. Cori, C. F., and Cori, G. T.: The Carbohydrate Metabolism of Tumors: II. Changes in the Sugar, Lactic Acid, and CO_2-Combining Power of Blood Passing Through a Tumor, J. Biol. Chem. **65**:397, 1925.

3. Carrel, A., and Ebeling, A. H.: The Fundamental Properties of the Fibroblast and the Macrophage: III. The Malignant Fibroblast of Sarcoma 10 of the Crocker Foundation, J. Exper. Med. **48**:105, 1928.

It is not enough to postulate the existence of a "Wund- or Teilungshormon," as Haberlandt [4] has done, or to assume the directive influence of an "archusia" and "ergusia," as Burrows [5] has done. These are mere words, and words have yet to solve a scientific problem. What is necessary is information as to the chemical groups concerned. Studies in this direction were undertaken at this institute about two years ago.

EVOLUTION OF THE SULPHYDRYL HYPOTHESIS

It occurred to me that the metal lead might serve as a reagent for identifying the growth-promoting stimulus, since Bell [6] had reported that growth is retarded thereby, and since lead is commonly used as a precipitant of biologic agents.[7]

It was first necessary to determine if the inhibitive influence of lead is exerted on growth by increase in cell number or on growth by increase in cell size.

It was found that the metal specifically retards cell proliferation and not cell assimilation.[8] Further, it was found that a well defined deposit of a lead-containing compound occurred in the regions of active cell division,[9] and that this concentration was associated with the nuclear activity of mitosis.[10] These data led to the conclusion that the metal, by precipitation, removes from activity some compound essential to cell reproduction.

Chemical studies under the microscope and of extracts in vitro brought out the fact that the lead-containing compound deposited in the region of active cell proliferation is a combination between the metal and sulphydryl. This, taken with the fact that sulphydryl is also found

4. Haberlandt, G.: Ueber Zellteilungshormone und ihre Beziehung zur Wundteilung, Befruchtung, Parthenogenesis und Adventivembryonie, Biol. Zentralbl. **42**:145, 1922.

5. Burrows, M. T.: Studies on the Nature of the Growth Stimulus in Cancer, J. Cancer Research **10**:239, 1926.

6. Bell, W. B., and Patterson, J.: The Effect of Metallic Ions on the Growth of Hyacinths, Ann. Applied Biol. **13**:157, 1926.

7. Hopkins, F. G.: An Autoxidizable Constituent of the Cell, Biochem. J. **15**:286, 1921.

8. Hammett, F. S.: Studies in the Biology of Metals: IV. The Influence of Lead on Mitosis and Cell Size in the Growing Root, Protoplasma **5**:535, 1929. Hammett, F. S., and Wallace, V. L.: Studies in the Biology of Metals: VII. The Influence of Lead on the Development of the Chick Embryo, J. Exper. Med. **48**:659, 1928.

9. Hammett, F. S.: Studies in the Biology of Metals: I. The Localization of Lead by Growing Roots, Protoplasma **4**:183, 1928.

10. Hammett, F. S.: Studies in the Biology of Metals: III. The Localization of Lead Within the Cell of the Growing Root, Protoplasma **5**:135, 1928. Hammett, F. S., and Justice, E. S.: Studies in the Biology of Metals: V. The Selective Fixation of Lead by Root Nuclei in Mitosis, ibid. **5**:542, 1929.

concentrated in the regions where growth by increase in cell number is enhanced, led to the hypothesis that the nuclear activity of cell division is importantly factored by sulphydryl (—SH).[11]

The next step was to test the hypothesis.

EXPERIMENTAL DATA IN SUPPORT OF THE SULPHYDRYL HYPOTHESIS

By a variety of rigidly controlled tests made with extracts, and with synthetic and naturally occurring sulphydryl compounds, on both plant and animal material, it was definitely established that the sulphydryl group is stimulative to cell division specifically, growth by assimilation not being accelerated. This result, taken together with the work as a whole, has led to the conclusion that sulphydryl is the essential stimulus to growth by increase in cell number.[12] A large mass of correlated data, reviewed in the paper cited, is thoroughly consistent with this conclusion.

Having thus identified a definite chemical group as specifically important in cell proliferation, the next step was to see whether or not the chemical data from the field of malignancy agree therewith, to see whether or not the etiologic concepts are explicable thereby, and tentatively to postulate an interpretation that might be used as a starting point for further exploration.

The chemical studies of sulphur metabolism in malignancy are meager and scientifically not all that is desired. Adequately controlled investigations of the sulphur partition in blood and urine are needed. What data there are have been collected in the admirable monograph of Kahn and Goodridge.[13] They indicate that the neutral sulphur fraction of the total sulphur is enhanced. Since this is composed of volatile sulphides, cysteine, cystine and similar suboxidized forms, the crude observations thus far made are consistent with the hypothesis that malignancy basically is the result of a distortion of sulphydryl equilibrium.

These gross observations may by no means be taken as specifically diagnostic. Other diseases show a like distortion of the sulphur excretion. This does not mean that the observations have no significance and should be discarded. On the contrary, their very inadequacy should stimulate investigations not only of the nature of the components of the neutral sulphur fraction, but also of the relative quantities in different diseases. This field needs cultivation.

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11. Hammett, F. S.: Studies in the Biology of Metals: VI. The Nature of the Lead Compound Deposited in the Growing Root, Protoplasma **5**:546, 1929.

12. Hammett, F. S.: The Chemical Stimulus Essential for Growth by Increase in Cell Number, Protoplasma, 1929, vol. 7.

13. Kahn, M., and Goodridge, F. G.: Sulfur Metabolism: A Review of the Literature, Philadelphia, Lea & Febiger, 1926.

Consistent with the finding of a relative increase in the excretion of neutral sulphur is the report of Roffo [14] that in animals with tumor the reducing power of the blood serum increases along with the tumor. This is probably not due to increase of sugar,[15] but to increase of sulphydryl-containing compounds.[16]

When it comes to the chemical analysis of tumor tissue, the data are more satisfactory. Although the values for total sulphur are inadequate for the drawing of any conclusion, since proper controls were not had, they do show a trend toward increased amount.[13]

They thus are consistent with the idea of an association between malignancy and sulphydryl.

The really significant observations are those of Voegtlin and Thompson.[17] These careful and competent investigators demonstrated that the living part of tumor tissue contains high concentrations of sulphydryl. In fact, the amounts were comparable to those present in the liver, one of the organs richest in this chemical group. Although Yaoi and Nakahara [18] did not obtain like results, the results of Voegtlin and Thompson have been definitely confirmed by Lecloux, Vivario and Firket,[19] and the relation can be considered as established.

Indirect evidence that sulphydryl is concentrated in tumor tissue is also available. Roffo and Correa [20] succeeded in isolating an insulinoid substance from malignant growths. The significance of this lies in the fact that insulin has been shown to contain suboxidized sulphur [21] and to be stimulative of cell proliferation in old ulcers of the leg,[22] though I found it unreactive for roots and paramecia.[12]

Further, Russell and Gye [23] observed that the oxygen consumption of cancerous tissue in the mouse rises with increasing speed of growth,

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14. Roffo, A. H.: Poder reductor del suero de ratas con tumores malignos, Bol. Inst. de med. exper. para el estud. y trat. del cáncer **4**:24, 1925.

15. Theis, R. C., and Stone, W. S.: A Study of the Chemical Composition of the Blood in Cancer, J. Cancer Research **4**:349, 1919.

16. Hunter, G., and Eagles, B. A.: Non-Protein Sulfur Compounds of Blood: II. Glutathione, J. Biol. Chem. **72**:133, 1926.

17. Voegtlin, C., and Thompson, J. W.: Glutathione Content of Tumor Animals, J. Biol. Chem. **70**:801, 1926.

18. Yaoi, H., and Nakahara, W.: The Glutathione Content of Chicken Sarcoma, Biochem. J. **21**:1277, 1927.

19. Lecloux, J.; Vivario, R., and Firket, J.: Teneur en glutathion du sarcome et des tissues normaux, Compt. rend. Soc. de biol. **97**:1823, 1927.

20. Roffo, A. H., and Correa, L. M.: La existencia de insulinoides en los tumores malignos, Bol. Inst. de med. exper. para el estud. y trat. del cáncer, 1926, no. 14.

21. Du Vigneaud, V.: The Sulfur of Insulin, J. Biol. Chem. **75**:393, 1927.

22. Aldersberg, D., and Perutz, A.: Beeinflüssung der Regenerationsfäbrigkeit der Haut durch lokale Applikation von Insulin, Klin. Wchnschr. **6**:108, 1927.

23. Russell, B. R. G., and Gye, W. E.: The Oxygen Consumption of Normal and Cancerous Mouse Tissues in Vitro, Brit. J. Exper. Path. **1**:175, 1920-1921.

and Warburg, Wind and Negelein [24] found that a diminution of oxygen supply below a certain level kills tumor cells within the body. This heightened demand for oxygen is what would be expected from the fact of increased concentration of sulphydryl. For, as shown by Hopkins and Dixon,[25] the sulphydryl group is a reducing group, avidly taking up oxygen and going over to the —S.S.— form.

Finally, Mueller [26] reported that the rapid auto-inactivation of the filtrate of the Rous fowl sarcoma is due to oxidation. Such oxidation may be prevented by cysteine. Oxidation produces in compounds containing sulphydryl a like loss of the activity stimulative of cell proliferation.[12] Also, Harde [27] reported that the virulent activity of Rous sarcoma is lost in alkaline solutions, but intensified by appropriate acidification. And it is a fact that the sulphydryl group is rapidly oxidized in alkaline mediums, but remains fairly stable in acid.[28] Thus, the sulphydryl group and the sarcoma virus behave alike as regards activity after autoxidation and exhibition to alkali. The concordance is noteworthy. Although it may be that the active agent of the Rous virus is itself not sulphydryl, the foregoing data indicate that its effectiveness is related thereto.

These several data make necessary a serious consideration of the hypothesis that a heightened sulphydryl reactivity of the tumor-producing cells is an important factor in, if not the fundamental cause of, tumors.

INTERPRETATION OF PRESENT ETIOLOGIC CONCEPTS OF MALIGNANCY IN TERMS OF THE SULPHYDRYL HYPOTHESIS

There are two possibilities. The cells that proliferate to malignancy are either inherently abnormally productive of sulphydryl or abnormally sensitive thereto.

The first possibility has but little experimental or observational support. Further, it yields no satisfactory explanation of the nature, etiology and diverse manifestations of tumors.

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24. Warburg, O.; Wind, F., and Negelein, E.: Metabolism of Tumors in the Body, J. General Physiol. **8**:519, 1928.

25. Hopkins, F. G., and Dixon, M.: On Glutathione: II. A Thermostable Oxidation-Reduction System, J. Biol. Chem. **54**:527, 1922.

26. Mueller, J. H.: The Effect of Oxidation of Filtrates of a Chicken Sarcoma (Chicken Tumor I-Rous), J. Exper. Med. **48**:343, 1928.

27. Harde, E.: The Influence of an Acid Reaction on the Virus of the Chicken Sarcoma (Rous) and Its Importance in the Experiments of Dr. Gye, J. Trop. Med. **29**:159, 1926.

28. Tunnicliffe, H. E.: Glutathione: Reactions Between the Tissues and the Oxidized Dipeptide, Biochem. J. **19**:199, 1925.

The increased concentration of sulphydryl in living tumor tissue might be taken as evidence of an inherent trend to overproduction. Opposed to this is the fact that, by and large, cell proliferation is confined to the tumor and does not spread to contiguous tissue. If sulphydryl were being produced in abnormally high concentrations, it might be expected that adjacent tissues would respond hereto [29] with growth by cell division; and this does not occur. Further, there is the fact that in growing animals the concentration of sulphydryl is highest in the youngest and gradually declines with age, as growth by cell division subsides.[30] Finally, it is a fact that in regions where active normal growth by cell reproduction is taking place, the concentration of sulphydryl is high.[11] From this, it follows that the high concentration of sulphydryl in malignant tissue is due to the fact that the cells are proliferating cells. The idea that tumor cells are abnormally productive of the stimulating group is unsustained.

The increased reducing power of the blood [14] and the increase in the neutral sulphur fraction of the total sulphur of the urine [13] might also be taken as evidence of an overproduction of sulphydryl by the malignant growth. But it can also be assumed that malignancy is an expression of a distortion of the cellular response to sulphydryl. It is, therefore, not unreasonable to suppose that there is inherent in those who are subject to malignant growths a tendency to a basic distortion of sulphur metabolism. From this, it follows that the picture in the blood and the urine may be but an expression of this perversion rather than an expression of an overproduction of sulphydryl from the tumor as such.

This interpretation implies no neglect of the fact that other diseases produce a similar gross picture. On the other hand, it is well known that different causes may produce the same physiologic effect. This arises from the fact that the end-results of reaction to diverse stimuli are limited by the biochemical mechanisms concerned in the general metabolic processes. Similarity in type of response is no proof of identity in the initiating agent. Since this statement is founded on fundamentals, it is valid until disproved by adequate investigation.

The available evidence having proved insufficient to establish whether or not malignant growth is a consequence of an abnormal productivity of sulphydryl by the tumor-forming cells, it remains to examine the

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29. Hammett (footnote 12). Gurwitsch, A.: Das Problem der Zellteilung physiologisch Betrachtet, Monograph aus der gesamtgeschichte der Physiologie der Pflanzen und der Tiere, no. 11, Berlin, Julius Springer, 1926.

30. Thompson, J. W., and Voegtlin, C.: Glutathione Content of Normal Animals, J. Biol. Chem. **70**:793, 1926. Murray, H. A., Jr.: Physiological Ontogeny: A. Chicken Embryos: IX. The Iodine Reaction for the Quantitative Determination of Glutathione in the Tissues as a Function of Age, J. General Physiol. **9**:621, 1926.

alternative, that the malignant growth is based on an abnormal sensitivity of the tumor-forming cells to sulphydryl.

This, perhaps, can best be done from the point of view of the more important etiologic concepts of malignancy.

Biologically, the etiologic factors of malignancy, as presented by Ewing [31] and Loeb,[32] are separable into two groups, the constitutional and the acquired.

All persons during the course of years are subjected to one or more of the tumor-inciting agents. But all persons do not incur malignant growths. The only possible conclusion is that susceptibility to the disease is constitutionally determined.

Countless clinical records attest the fact that the inception of many malignant growths is an antecedent irritation. Since the constitutional make-up is inborn and present before the reception of the tumor-evolving agent, it is clear that the initiation of malignancy depends on the application of an adequate stimulus. The constitutional factors provide the ground on which the acquired factors exert their influence. Only the combination results in malignancy.

The following classification provides a useful basis for analysis:

A. Constitutional factors
   1. Heredity
   2. Cell autonomy
   3. Internal secretion
   4. Embryonal (congenital)

B. Acquired factors
   1. Irritation
      (*a*) Mechanical
      (*b*) Physiologic
      (*c*) Chemical
      (*d*) Parasitic

Heredity.—The difference between persons who bear tumors and those who do not is a constitutionally determined difference in the nuclear activities related to cell proliferation. This difference expressed in malignancy is an inheritable characteristic. The work of Loeb,[33] Slye,[34] Little [35] and others can yield no other conclusion.

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31. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

32. Loeb, L.: Causes and Definition of Cancer, Am. J. M. Sc. **159**:781, 1920.

33. Loeb, L.: Heredity and Internal Secretion in the Etiology of Cancer. Internat. Conference on Cancer, London, 1928, p. 48.

34. Slye, M.: The Relation of Cancer to Heredity with Regard to the Communication of President C. C. Little of the University of Michigan, J. Cancer Research **12**:83, 1928.

35. Little, C. C.: Evidence that Cancer Is not a Simple Mendelian Recessive, J. Cancer Research **12**:30, 1928.

My experimental work justifies the belief that sulphydryl is specifically essential to the nuclear processes of cell division.[12] As is well known, these are integrated by the chromosomes, and the chromosomes are the determinants of the inherited characteristics. Therefore, the factor of heredity would be a determinant of the level of nuclear response to sulphydryl.

These considerations and the known correlation between malignancy and sulphydryl lead to the conclusion that the inheritability of malignancy is conditioned, if not determined, by an inbred shift in nuclear reactivity to sulphydryl. The data are thus consistent with the assumption that malignancy results from an abnormal sensitivity of the tumor-producing cells to sulphydryl.

Cell Autonomy.—Many side issues are included in the consideration of this constitutional factor as discussed by Ewing.[31] They all boil down to the question of the inherent proliferative properties of the cancer cell, and the relation of the tissue environment thereto.

Some preliminary definition is necessary.

The inherent proliferative energy of cells has nothing to do with the total possible number of cells producible, for this is limitless, as the studies of Carrel [36] and Woodruff [37] prove. Nor has it anything directly to do with the rate of formation of new cells, since this is largely controlled by environmental factors.[38] Its sole property is the determination of the nuclear threshold of response to proliferative stimulation. This is a matter of constitutional makeup or heredity and is related to the sensitivity to sulphydryl, as shown in preceding paragraphs. The concept is thus in agreement with the assumption of the greater sensitivity of the malignant cell to sulphydryl.

The other chief item in the bracket for cell autonomy is the question of restraints on growth. These can be considered under three headings: architectural, cytologic and chemical.

The histologic point of view has been adequately discussed by Reimann in the aforementioned paper, in which he shows that the diverse architecture of malignant growths is essentially a consequence of the diverse anatomic and physiologic environments in which the proliferation of cells takes place. The architecture, then, is no index of the inherent proliferative capacity of the growth. It merely shows what the growth can do in the particular environment in which it occurs. Hence it is only of supplementary significance in etiology.

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36. Carrel, A.: Tissue Culture and Cell Physiology, Physiol. Rev. **4**:1, 1924.

37. Woodruff, L. L.: Eleven Thousand Generations of Paramecium, Quart. Rev. Biol. **1**:436, 1926.

38. Gurwitsch (footnote 29, second reference).

As discussed by Reimann, the cytologic status resolves itself into the question of the relation of cell size to rate of malignant growth, and the stage of cell development at the time of proliferation in its bearing on the type of tumor produced. The latter is essentially an architectural matter; but the former is directly relatable to the interpretation of malignancy in terms of sulphydryl.

It has been found that in a cell population where growth by increase in cell number and growth by increase in cell size are taking place simultaneously, small cell size is associated with increased rate of cell division.[39] And the pathologists have observed that small cell size is generally indicative of a high degree of malignancy as established by subsequent history. Thus, cytologically, in both normal and pathologic material, cell size is a rough index of the extent of the autonomous restraint on growth.

The parallelism demonstrates that the phenomena of cell size in malignancy are on the same biologic basis as are those of normal growth by increase in cell number, when and if the masking influences of environmental factors are properly accounted for. On the basis of the experimental data cited, it is clear that this relationship is further evidence in support of the assumption under discussion.

As to the matter of autonomous chemical restraints on growth it is obvious that such exist. The work of Carrel [36] and others with tissue cultures proves that unlimited proliferation of cells will not occur unless the products of the growth reaction are repeatedly removed from the scene. There are, thus, restrictive and stimulative factors of cell division through which equilibrium is maintained in the normal person. From what has gone before and from purely chemical considerations based on the law of mass action, it can be asserted that cell proliferation is regulated by a chemical equilibrium in which sulphydryl is the key group. From this, it follows that the autonomous chemical restraints on growth by increase in cell number are, in all probability, products of the oxidation of sulphydryl.[12]

The assumption that malignancy is the result of an unusual sensitivity of the tumor-producing cells to sulphydryl is supported by this concept. For, on the basis of the equilibrium hypothesis it is clear that if the threshold of response to inhibition is raised, as it surely is in malignancy, then the threshold of response to stimulation must be lowered, else no unusual proliferation of cells would take place. In other words, the point of equilibrium is shifted toward the sensitivity to R-SH side of the equation.

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39. Hammett, F. S.: Cell Division and Cell Growth in Size, Protoplasma, to be published.

This is sufficient and all that is necessary to indicate that the major concepts in the bracket of cell autonomy in malignancy are interpretable in terms of sensitivity to sulphydryl.

Internal Secretion.—Next in the order of importance of the constitutional factors of malignancy is internal secretion. At present, the evidence justifies the inclusion of but one incretory organ in the group. This is the ovary. The others have no proved influence, save the thyroid gland.

The influence of ovarian incretory activity is a purely constitutional factor, since the ebbing and flowing of this is a normal phenomenon of the female. In the etiology of tumor, it is the most important constitutional factor next to heredity and cell autonomy, since the majority of malignant growths in the female are traceable thereto.

At present there is no evidence justifying the designation of the thyroid gland as a purely constitutional factor in the sense that shifts in its level of activity within usual limits are etiologic factors in malignancy. It is only of demonstrable significance when it has acquired an abnormal level of functional activity. This is usually a consequence of exogenous stimulation.[40] Hence the rôle of the organ in malignancy is logically to be considered under the heading of acquired factors, until it is shown that an etiologic relationship is present within the usual range of the functional level.

Loeb [41] conclusively demonstrated the fact which Cori [42] and others confirmed—that ovarian incretory activity is of great significance in the production of mammary carcinoma in mice. In fact, Loeb stated that the realization of the hereditary tendency to cancer presupposes the activity of the internal secretion of the ovary. Without this cooperation no cancer can originate.

Statistical records show that malignant growths occur most frequently in women in just those organs subjected to periodic ovarian stimulation.

In the aforementioned paper, Reimann described, with absorbing interest, the histologic changes that take place in the human breast under ovarian stimulation during the recurrent menstrual cycles. He wrote, "In the normal breast there is a constant reciprocal growth and recession of epithelium and connective tissue." Biochemically, this means that the breast is periodically subjected to a flooding with cellu-

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40. Hammett, F. S.: Thyroid and Growth, Quart. Rev. Biol., to be published.

41. Loeb, L.: Quantitative Relations Between the Factors Causing Cancer and the Rapidity and Frequency of the Resulting Cancerous Transformation, J. Cancer Research **8**:274, 1924.

42. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas in Mice, J. Exper. Med. **45**:983, 1927.

lar disintegrative products. From the work of Bierich and Kalle [43] it is known that catabolic processes similar to this are liberative of sulphydryl from the protein-bound unreactive state to the free condition in which characteristic action is possible.

Now all breasts are subjected to this stimulus to the proliferation of cells, but all breasts do not respond by a cancerous overgrowth. In most, the cellular regeneration stops short of this point. The valid implication is that in those in which cancer does develop the threshold of sensitivity to sulphydryl is lower than usual. The facts, as a whole, are consistent with this hypothesis, and permit an extension of its application to those other tumor-producing organs that are subject to periodic ovarian stimulation.

There is no space here to go into Loeb's [41] rigidly critical analysis of the etiology of cancer of the breast. Those who are interested enough to study his admirable paper will find in the sulphydryl hypothesis an explanation of the principles therein set forth.

Embryonic Rests.—Cohnheim's dictum that cells retaining embryonal characteristics are significant agents in the etiology of tumor is too well attested by comparative observations to be questioned. The usual conception is that these so-called embryonal rests are the result of a congenital distortion of differential development. This is probable in such cases as Albrecht's hamartoma and the like. On the other hand, it is also possible that the majority of cases derive from one or more lines of cells in which embryonal characteristics, so far as proliferative potentialities are concerned, are retained because of hereditary forces. These lines can be considered as minority contributors to the mass building of tissues and organs and thus they provide foci from which malignant growths may arise on adequate stimulation.

This conception, which as a possibility has no genetic negation, provides a more satisfactory explanation for most of the tumors classed as embryonal than does that of congenital distortion. Both ideas, however, stress the fact of the origin of tumors from cells retaining embryonic characteristics of cell proliferation. Experimental evidence supporting the assumption is had from the serologic studies of Gruskin.[44] This worker apparently demonstrated a homologous relationship between embryonic and malignant cells by amboceptor and antigen reactions with mammalian embryonic epithelium and connective tissue.

The studies of Müller [45] lend support to this view. He found a close histologic correspondence between epithelial regeneration in wounds

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43. Bierich, R., and Kalle, K.: Untersuchungen über das Zustandekommen der bösartigen Geschwülste, Ztschr. f. physiol. Chem. **175**:292, 1928.

44. Gruskin, B.: A Serum Test for the Diagnosis of Cancer Based on a New Theory of Etiology, Am. J. M. Sc. **177**:476, 1929.

45. Müller, H.: Die histologische Uebereinstimmung zwischen Epithelregeneration und Krebsbildung, Ztschr. f. Krebsforsch. **28**:383, 1929.

and cancerous organization. Yet in the one case only normal repair occurs, while in the other the cells proliferate to malignancy. There is, thus, a fundamental difference in their reaction to stimulation, which is interpretable only on the basis of the foregoing hypothesis. Müller's observations are also in line with those of Carrel on tissue cultured fibroblasts. For this latter worker reports that no histologic, only metabolic, differences are ascertainable.

The concept is fittingly interpretable from the point of view of a low threshold to sulphydryl. For it has been found in this institute, in working with chick embryos, that the regions of most active growth by increase in cell number are most stimulated to proliferation of cells by sulphydryl. That is to say, the more embryonal the cells are, as evidenced by their more rapid rate of division,[46] the more sensitive they are to sulphydryl.

The fact that all malignant growths are expressions of but one fundamental biologic phenomenon, i.e., cell proliferation, makes it imperative that any interpretation of the basic etiology of tumor be also founded on a single principle.

The foregoing analysis of the constitutional factors shows this condition to have been satisfied. From it comes the conclusion that the potentiality for malignancy lies in the hereditary determination of lines of cells retaining the embryonic characteristic of a heightened sensitivity to the essential cell proliferation stimulus, sulphydryl.

The chief phenomena of malignancy fit in with this concept.

There is no evidence, save in rare instances, that the cells of a malignant growth possess the functional properties of the organ from which they originate. This is significant. It means that if the ontogenetically mature cells of the organ become tumor-producing cells they dedifferentiate in the process; or it means that the growths arise from cells of hereditarily determined embryonic characteristics, and hence, because of their low ontogenetic level, cannot go on to normal differentiation.

The dedifferentiation can be rejected on the grounds of the work of Lewis and Lewis [47] with tissue cultures. On the basis of the alternative implication, the phenomenon is consistent with the premise of this discussion.

The fact of metastasis is evidence for the idea discussed by Reimann from the point of view of stroma reaction, that tumor cells are not

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46. Minot, C. S.: The Problem of Age, Growth, and Death, New York, G. P. Putnam's Sons, 1908.

47. Lewis, W. H., and Lewis, M. R.: Behavior of Cells in Tissue Cultures, in Cowdry, E. V.: General Cytology, Chicago, University of Chicago Press, 1924, pp. 383-448.

foreign cells. Further, the cells of the metastases increase in number, but those of the diverse supporting tissue rarely give evidence of tumor-like cell multiplication. These facts indicate that the metastatic cells are lines of body cells in which the embryonic characteristic of a low threshold to the stimulus of proliferation is retained. Further, the fact that the liver and the lymph nodes are common seats of metastasizing growths is significant in that the former is the organ of the highest natural sulphydryl content [30] and the latter are foci of cell multiplication. Thus, the phenomenon fits in with, and is support for, the conclusion that has been drawn.

Now it is not unreasonable to suppose that lines of cells with this low threshold may separate at any one of the several earliest stages of the development of the egg before the organic patterns have made their appearance. This may be conceived of as occurring, in some cases, before cellular differentiation has proceeded far, perhaps not much beyond the period of the three germ layers. In others, the separation may take place at the time of the formation of the organ anlage.

In the first case, a general dissemination of the potentially malignant cells would be predicted according to the germ layer in which they have their origin. In the second, the potentiality would be restricted to the organ from the anlage of which the cells derived. If these considerations are correct, it follows that both a general and a local predisposition to tumor on adequate stimulation are to be expected. Since such predispositions do occur, as exemplified in the first and third cases cited by Reimann, it is clear that the facts fit the theory, and further support is had for the interpretation of the constitutional factors of malignancy in preceding paragraphs.

The question may properly be raised, if the potentiality for malignancy lies in hereditarily determined lines of cells of low threshold to sulphydryl, why do the majority of tumors fail to arise until long after normal growth by increase in cell number has ceased? Surely, since in the early stages there is an adequate concentration for the multiplication of normally constituted cells, there is more than enough for the multiplication of the potentially tumor-producing cells of high sensitivity.

Now the thesis has been developed from experimental observations that growth by increase in cell number is a self-regulated chemical process in which sulphydryl is the key group. This is the essential stimulus. The inhabitant is taken to be an as yet unidentified product of the oxidation thereof, arising in the natural course of the chemical processes concerned in cell division.[12] Since normal cells numerically predominate during the developmental period as in the adult, their mass production of the inhibitant of proliferation is conceivably the means of holding in check the minority of low-threshold, tumor-potential cells.

As development proceeds, the concentration of sulphydryl decreases concomitantly with growth by increase in cell number,[48] while the concentration of the chemical inhibitants presumably increases. Thus, less and less favorable conditions for the expression of the tumor-producing potentiality develop, until at adulthood the concentration of sulphydryl is below the stimulative level. Until and unless this is increased to an adequate concentration, malignancy does not develop. This is the interpretation of latency.

Anemia of Malignancy.—The anemia that occasionally accompanies certain types of malignant disease is also explicable in terms of sulphydryl. Here, however, the apparent exceptions make the interpretation more suggestive than conclusive. On the other hand, it is worth a thought.

The explanation is based on two facts. The first is that sulphydryl is essential to cell proliferation.[12] The second is that as tumors grow larger the sulphydryl of the rest of the body declines.[17] The implication, then, is that tumor growth lowers the concentration of sulphydryl in the bone-marrow and thus the formation of red cells is dampened. Consistent with, but not proof for, the idea is the fact that liver, which stimulates erythropoiesis, has a high sulphydryl content,[30] and the fact that the concentrated active agent from liver has a high cystine content.[49]

Irritation: Mechanical Injury or Trauma.—It is now possible to turn to the discussion of the acquired factors of malignancy without which no tumor is possible. Those which have been proved to be effective properly come under the heading of irritation, when this term is used in the broad sense of Verworn. That is to say, mechanical, physiologic, chemical and parasitic actions are able to produce a state of irritation that, in a constitutionally prepared person, results in malignancy. This state of irritation, however, is but the expression of an underlying disruption of a previously existing chemical equilibrium.

In the light of this fact, one is in a position to examine the data available with respect to the various inciting agents and see whether they fit the concept that sulphydryl is a necessary participant in the development of malignant disease.

No one will question that many malignant growths are traceable to an antecedent contusion. Nor will any one question that cellular disintegration or autolysis follows such injury. Therefore, since Bierich and Kalle [43] have shown that previously bound sulphydryl is liberated in free form on tissue autolysis, it can be postulated that an increased concentration of this group arises on traumatization.

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48. Mueller (footnote 26). Thompson and Voegtlin (footnote 30, first reference).

49. Looney, J. M.: The Analysis of Liver Extract, J. Biol. Chem. **78**:11, 1928.

Direct and indirect evidence, as well as inferential, is at hand. Reiche [50] found that tissue autolysates favor mitosis. Haberlandt [4] observed stimulation of cell division after injury. Giroud and Bulliard [51] noted an association between sulphydryl concentration in the skin and keratinization, while Lightbody and Lewis [52] confirmed this principle on dietary grounds. Significantly, Carnot and Terris [53] got remarkable healing of cutaneous wounds by extracts of proliferating skin. Finally, I have consistently obtained a marked intensification of the nitroprusside test for sulphydryl on injury of root-tips, either by crushing or by scratching.[11]

All these facts lead to the one conclusion that trauma liberates sulphydryl, which then acts as a stimulus to cell proliferation. The fact that trauma is frequently productive of malignancy is, thus, strong support for the theory being developed in this paper.

Physiologic Irritation.—This discussion is purposely limited to data derived from experimental and clinical observation. Speculation without such a basis is unwarranted under the present circumstances. Because of this, consideration of the physiologic factors of malignancy is restricted to the internal secretion of the thyroid gland. No other physiologic activity gives even a suggestion of being an acquired factor in the development of malignant disease. Even in the case of the secretion of the thyroid gland the evidence is circumstantial. The observations, however, are sufficiently numerous, and the explanation, therefore, is sufficiently consistent with the whole background, to justify the postulation of a relationship as a generalization.

Dercum,[54] in a stimulating analysis, reviewed the data on the clinical association between thyroid activity and malignancy. The sum and substance of his collected observations is that malignant disease is infrequent, if not rare, in persons suffering from hyperthyroidism.

This negative correlation might be predicted from the known facts relative to thyroid function and sulphydryl lability. For it is well known that the metabolic rate is regulated by the level of thyroid activity, and that when this is increased, the oxidative processes of the body are

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50. Reiche, H.: Ueber Auslösung von Zellteilung durch Injektion von Gewebsäften und Zelltrümmen, Ztschr. f. Bot. **16**:241, 1924.

51. Giroud, A., and Bulliard, H.: Glutathione et kératine, Compt. rend. Soc. de biol. **98**:500, 1928.

52. Lightbody, H. D., and Lewis, H. B.: The Metabolism of Sulfur: XV. The Relation of the Protein and Cystine Content of the Diet to the Growth of Hair in the White Rat, J. Biol. Chem. **82**:485, 1929.

53. Carnot, P., and Terris, E.: Sur la cicatrisation de plaies cutanées par les extraits d'embryons de peau régenerée, Compt. rend. Soc. de biol. **95**:655, 1926

54. Dercum, F. X.: The Biological Interpretation of Malignancy, Cancer J. **2**:97, 1925.

enhanced.[40] Further, it is a fact that the sulphydryl group is exquisitely sensitive to oxidizing agents.[25] Hence, other things being equal, the chance for the development in a person with hyperthyroidism of a sulphydryl concentration adequate to produce malignant cell proliferation is limited. Other supportive argument could be made, but this is sufficient to establish the consistency of the phenomenon with the general thesis.

Chemical Irritation.—Malignant cell proliferation is also directly initiated by chemical substances, particularly those related to the tarry by-products of the distillation of coal and petroleum. Apparently, two factors are responsible here: (1) repeated irritation, which may be produced either by friction or by irritating substances in the tars, and (2) the presence of the tarry products themselves.

When such agents give rise to truly metastasizing malignant growths, a constitutional predisposition is undoubted. In many cases, however, the growths do not progress after the removal of the exciting agent and may even regress. They also fail to recur when surgically extirpated if the subject comes in no further contact with the stimulus to cell proliferation, even though similar irritation is produced. In these cases, a constitutional predisposition is questionable. Rather is the original growth attributable to the presentation to the irritated cells of an extraordinary concentration of cell proliferation stimulus from tar constituents over and above that liberated by the injury. This is the logical deduction from the pertinent data. Biologically, the principle is fundamentally correct, for it has been found that the experimental increase in the normal cell multiplication stimulus, sulphydryl, causes an acceleration of normal cell division.[12]

The residues of the distillation of both coal [55] and petroleum [56] are characterized by significant percentages of mercaptans and sulphides; the oils themselves, of course, likewise.

In view of all that has gone before, it is reasonable to assume that the tar and allied cancers are but the proliferative reaction of irritated tissues to a concentration of sulphydryl above that necessary for normal cell division repair.

Sustaining evidence for this conclusion is had. It has been found that tumors cannot be produced experimentally by any and every tar, but that only certain products are effective. This is associable with the fact that petroleum from different localities contains widely different percent-

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55. Stadnikov, G.; Gravilov, N., and Rakovskii, V.: Desulfurization of Cresols and Acid Fractions of Various Coal Tars, Brennstoff. Chem. **7**:65, 1926. Mailhe, A.: Sulfur Compounds in Coal Tar, J. usines gaz. **41**:209, 1921.

56. Day, D. T.: Handbook of the Petroleum Industry, New York, John Wiley & Sons, 1922.

ages of labile sulphur compounds, ranging from negligible to significant amounts.[57]

The picture is consistent with the general concept of the relation of sulphydryl to malignancy.

The foregoing interpretation might be objected to on the observation of Murphy and Landsteiner [58] that a sarcoma produced in the chicken by the combined injection of tar and embryonic tissue is transplantable through succeeding generations. But so are other, spontaneously occurring chicken tumors.[59] This latter fact would indicate that there is a constitutionally determined ground for the development of tumor in the fowl susceptible to stimulation by appropriate agencies.

In the spontaneous tumors transmissible by filtrates and desiccates, this agent is, according to Murphy,[60] enzymic in nature and, hence, endogenous or constitutionally determined. Transmissibility, as well as transplantability, indicates that the activating agent is produced by the tumor cells themselves. The essential similarity of this with sulphydryl in its reactions has already been pointed out.

In the case of the tar tumor, the irritating agent is, in all probability, the labile sulphur, as discussed. Its nontransmissibility by filtrates or desiccates [61] should cause no wonder. In this case, an exogenous stimulus starts off a malignant growth in a constitutionally disposed animal, which is naturally transplantable into other similarly constitutionally disposed animals, but not transmissible since the irritating agent is not endogenous.

Parasitic Irritation.—The brilliant studies of Fibiger [62] with animals, and of Smith [63] with plants, make necessary the inclusion of parasitic organisms in the group of incitants to malignant growth.

In the case of *Spiroptera carcinomata,* indirect evidence brings the reaction in line with the general concept. The provocative organisms

57. Redwood, B.: Treatise on Petroleum, Philadelphia, J. B. Lippincott Company, 1922.

58. Murphy, J. B., and Landsteiner, K.: Experimental Production and Transmission of Tar Sarcomas in Chickens, J. Exper. Med. **41**:807, 1925.

59. Rous, P., and Lange, L. B.: The Characters of a Third Transplantable Chicken Tumor Due to a Filtrable Cause: A Sarcoma of Intracanalicular Pattern, J. Exper. Med. **18**:651, 1913.

60. Murphy, J. B.: The Nature of the Filtrable Agent in Chicken Tumors, Report of the International Conference on Cancer, London, 1928.

61. Sturm, E., and Murphy, J. B.: Further Observations on an Experimentally Produced Sarcoma of the Chicken, J. Exper. Med. **47**:493, 1928.

62. Fibiger, J.: On Spiroptera Carcinomata and Their Relation to True Malignant Tumors: With Some Remarks on Cancer Age, J. Cancer Research **4**: 367, 1919.

63. Smith, E. F.: Studies on the Crown-Gall of Plants: Its Relation to Human Cancer, J. Cancer Research **1**:231, 1916.

produce eggs in huge numbers. Shearer [64] found that on fertilization the concentration of free sulphydryl in the eggs of *Echinoderm* increases markedly. This reaction is probably general. Further, it is well known that nematodes have great regenerative capacities. Since this is a phenomenon of cell division presumably dependent on sulphydryl, it follows that here is a possible additional source of supply of the stimulus to cell multiplication. The idea, then, is that through production of eggs and fertilization of them, and the chemical stimuli of regeneration, *Spiroptera* provides a concentration of sulphydryl adequate to stimulate an abnormal proliferation of cells in a ground prepared by the inflammatory processes and constitutionally inclined to a pathologic response.

In the case of *Bacillus tumefaciens,* the data are also meager. Direct knowledge is had only of the first step in the reaction: that the organism excites inflammatory processes which, in constitutionally prepared persons, go on to malignancy.[65] Now, inflammation is the result of an injury,[66] and, as stated earlier, injury of plant root tissues results in liberation of free sulphydryl. Correlating these facts leads to the conclusion that the phenomenon is interpretable in terms of the generalization. It would be decidedly worth while to see whether or not *B. tumefaciens* possesses any specific type of sulphur metabolism that would be correlatable with its tumor-producing properties.

Studies with other parasites have thus far yielded no sure conclusion.[31] There are certain facts, however, which are suggestive in the light of the present interpretation. It is known that mercaptans and hydrogen sulphide are produced in the large intestine by the bacterial decomposition of protein food residues.[13] Miss Margaret Sharpe, working in this institute, found that both hydrogen sulphide and its disodium salt are effective stimulants of reproduction in *Paramecium caudatum.* Thus, there is present in the colon the chemical stimulus for a proliferation of cells as an acquired factor from bacterial activity. This is present in varying concentration. From this, it is obvious that conditions are frequently favorable for the development of malignancy in constitutionally susceptible persons. I am inclined to believe that this is often a potent factor in the genesis of rectal carcinoma. Contributory would be constipation, with its attendant accumulation of bacterial by-products and consequent irritation. The

64. Shearer, C.: Oxidation Processes of the Echinoderm Egg During Fertilization, Proc. Roy. Soc., London **93**:213, 1922.

65. Levin, I., and Levine, M.: Malignancy of the Crown-Gall and Its Analogy to Animal Cancer, J. Cancer Research **5**:243, 1920.

66. Rivera, V.: E necessaria la ferita del tessuto per la produzione di tumori da B. tumefaciens su vegetali? Boll. Accad. pugliese sc. **1**:1, 1926.

fact that about 60 per cent of the cases of constipation are proctogenic [67] supports this idea.

From this analysis of the mechanisms of the constitutional and the acquired factors in malignancy, it is clear that they are all reducible to a common basis. Thus the condition as outlined on an earlier page is satisfied, i. e., that any interpretation of the basis of tumor genesis must be founded on a single principle, since all malignancy is but the expression of one fundamental biologic phenomenon, namely, the proliferation of cells.

Further, the data in this bracket are support for the idea developed during the analysis of the constitutional factors, that the cells which proliferate to malignancy are abnormally sensitive to sulphydryl.

SUMMARY AND CONCLUSION

This synthesis has been based on the biologic principle that any satisfactory interpretation of malignant growths must be founded on a knowledge of the chemical stimulus to growth by increase in cell number.

The first step was a description of the experimental work leading to a demonstration that the sulphydryl group is the essential stimulus to multiplication of cells in healthy material. Direct transference of this observation to tumor tissue is allowable on the basis of Baker's [68] report that glutathione, a sulphydryl-containing compound, is stimulative of a proliferation of cells in tissue cultures of sarcomatous fibroblasts.

The next step was an examination of the available reports with respect to sulphur metabolism in general and sulphydryl in particular in tumor-bearing persons and tumor tissue. From this, it was seen that the correlative data consistently support the idea of an interrelationship between sulphydryl and malignancy.

The third step was an examination of the etiologic concepts of malignancy for the purpose of seeing whether or not they could be lined up on a common basis. From the known facts, the thesis was developed that malignancy, in general, is a product of a combination of constitutional and acquired factors. An analysis of these showed that their influence is interpretable in terms of sulphydryl.

The chief manifestations of malignancy were also tested against this concept and found to be sustaining thereof.

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67. Reimann, S. P.: The Pathological Physiology of Surgical Diseases by Prof. Dr. Franz Rost, Philadelphia, P. Blakiston's Son & Company, 1923.

68. Baker, L. E.: The Chemical Nature of the Substances Required for Cell Multiplications: II. Action of Glutathione, Hemoglobin, and Ash of Liver on the Growth of Fibroblasts, J. Exper. Med. **49**:163, 1929.

From all this the generalization has developed that the potentiality for malignancy lies in the hereditary determination of lines of cells retaining the embryonic characteristic of a heightened sensitivity to the essential stimulus to proliferation of cells, sulphydryl, and that the development of malignancy depends on the presentation to the potentially tumor-producing cells of an adequate concentration of this chemical group.

I am quite willing to admit that this interpretation is possibly not the last word in the apparently complex problem of malignant disease. On the other hand, it does suffice to bring some order out of a previously existing chaos. Its validity, of course, rests on the soundness of the biologic principles involved.

A REVIEW OF THE PLEURAL AND PULMONARY LESIONS IN TWENTY-EIGHT FATAL CASES OF ACTIVE RHEUMATIC FEVER*

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Clinically, lesions of the respiratory system have received considerable attention in rheumatic fever, as pleurisy and even pneumonia have been said to be common manifestations of this disease.[1] Nevertheless, the nature of these lesions is somewhat ill defined; the number of pathologic studies that have been brought to bear on them is small, and there are certain fundamental questions about the lesions which remain unanswered, such as the extent to which they are specific manifestations of rheumatic fever. In this disease, the respiratory system may be the seat of a variety of injuries. For example, besides pleurisy and bronchopneumonia, so often found in rheumatic fever, almost all the fatal cases exhibited pulmonary manifestations of failing cardiac function, frequently with the presence of transudate fluid in the chest cavities associated with varying degrees of pulmonary atelectasis, passive congestion, pulmonary edema, infarction, etc. Our primary purpose in this paper is to record the outstanding pulmonary changes observed in a series of fatal, active cases of rheumatic fever and, in our analysis of them, an attempt will be made to isolate those few lesions that we believe represent specific manifestations of this obscure disease.

Recent work embracing such a study of pathologic material in rheumatic fever includes that of Thayer,[2] who reviewed a series of twenty-five fatal cases of active rheumatic fever from the necropsy series of the Johns Hopkins Hospital. The author recorded pulmonary changes, but apparently he had not studied these in detail. All his cases showed pulmonary evidences of myocardial insufficiency. Terminal

* Submitted for publication, Jan. 4, 1929.

* From the Ayer Clinical Laboratory of the Pennsylvania Hospital.

* A more comprehensive review of the material reported in this paper is included in the 1928 Alvarenga Prize Essay of the College of Physicians and Surgeons, Philadelphia.

1. The literature on this subject has been reviewed in a recent article by Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine **7**:383, 1928.

2. Thayer, W. S.: Notes on Acute Rheumatic Diseases of the Heart, Bull. Johns Hopkins Hosp. **36**:99, 1925.

pneumonia or bronchopneumonia was noted in 40 per cent. The pleural lesions were not recorded.

A large series of cases of rheumatic fever in which necropsies were made was studied by Pappenheimer and von Glahn,[3] who paid particular attention to the vascular lesions. They did not offer detailed studies of the lungs, but reported the presence of lesions, in a small percentage of the cases, involving peripheral arteries, arterioles and capillaries in the pulmonary, as well as in the systemic, circulation.

Others[4] who have described the pulmonary changes in cases of rheumatic fever have found the most prominent lesion to be a diffuse "pneumonitis," consisting of an acute interstitial or perivascular, nonsuppurative type of inflammation, and have been struck with the resemblance between this lesion and the classic rheumatic lesion of the myocardium.

MATERIAL

The material on which our study is based was obtained from the necropsy series of the Pennsylvania Hospital. This series totaled, at the time, about 3,600 cases. In selecting cases for study, only those were included in which death had occurred during an active stage of the disease. The criterion of activity was the finding of Aschoff bodies in the myocardium (found in 85 per cent of the cases) together with endocardial and valvular lesions and also pericardial lesions. Cases in which there was an extensive ulcerative endocarditis associated with the presence of large numbers of bacteria were not included. In a few, however, tiny ulcerations were present on the cardiac valves together with typical rheumatic vegetations and, from three of these, hemolytic or anhemolytic streptococci were isolated.

Fourteen of the twenty-eight cases had occurred since 1922. These we had had the opportunity of studying first hand. The remaining fourteen were selected from the older series. Information concerning them was obtained from the protocols but more especially from our studies of the available tissue that had been preserved.

RESULTS

The different lesions encountered will be considered under a number of different headings.

Pleurisy.—Rheumatic pleurisy has been said to occur in from 5 to 10 per cent of clinical cases of rheumatic fever, usually accompanying rheumatic pericarditis and, as a rule, indicating a severe rheumatic infection. It does not seem to have been clearly defined, however; perhaps

3. Pappenheimer, A. M., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, J. M. Research **44**:489, 1924. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235, 1926.

4. Eiman, J., and Gouley, B. A.: Rheumatic Pneumonitis, Tr. Path. Soc., Philadelphia, Arch. Path. **5**:556 (March) 1928. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10 (July 7) 1928.

because one is loathe to accept the mere presence of fibrinous pleurisy or the accumulation of pleural fluid in this disease as an indication of a pleurisy that is essentially rheumatic.

In our series of cases, many of which represented that severe and fulminating form of rheumatic fever which occurs in children, active pericarditis was present at necropsy in 75 per cent, and active pleurisy in 64 per cent of the cases.

Three cases with active pleurisy, in which typical bronchopneumonia was present, have not been included in the discussion. Many others with diffuse focal hemorrhages in the lung gave a picture that might be classified as acute hemorrhagic bronchopneumonia, although the degree to which this lesion is related to the pleural one has not been determined. However, the characteristic feature of the latter group was that the pleural lesion was more extensive than that usually found in association with the common types of acute hemorrhagic lobular pneumonia. Furthermore, it was always nonsuppurative, and in none of the cases in which bacteriologic studies were made, were organisms demonstrated in direct association with it.

The type of nonsuppurative pleurisy that has been designated by many authors as rheumatic pleurisy bears a close resemblance to the pericardial lesion. In the material furnished by our cases, it showed the following characteristics:

Gross Appearances: As an early manifestation, small, focal collections of pinhead-sized petechial hemorrhages, similar to the epicardial or pericardial hemorrhages so frequently found in this disease, appeared on the visceral pleural surface, either with or without the presence of hemorrhagic lesions in the underlying pulmonary tissue.

A later stage, and this proved to be by far the commonest manifestation, was the appearance of fibrinous exudate on the pleural surfaces. This was noted in half the cases, and in most instances there was also an accumulation of fluid in the pleural cavity. Undoubtedly, many factors contributed to the accumulation of the fluid in the pleural cavity as a terminal event, but our studies pointed to a relatively specific type of injury to the pleura as playing a leading rôle in this. Certainly, the amount of fluid exudate, and its character, are closely related to the degree of inflammation of the pleura. Pleural fluid was present in eighteen cases of the series; in five, it exhibited the essential characteristics of a transudate and was associated with ascites and edema of the extremities; but, in the remaining thirteen, it was the accompaniment of a frank pleurisy with effusion. We shall limit our descriptions to these cases, which we believe presented the type of pleurisy peculiar to rheumatic fever.

The fluid will be described later.

The lungs were usually found moderately compressed, particularly in their dependent portions, and over these areas the pleura appeared slightly opaque. Pleural vessels and lymphatics were frequently dilated and opaque, and unusually prominent, often outlining individual lobules with a "chicken wire" effect. Closer inspection sometimes revealed a fine, thin film of fibrin covering certain areas of the lung. As the process advanced, and particularly in those cases in which an

excess of fluid had accumulated, the surfaces sometimes appeared opaque and roughened, with strings of fibrin traversing the cavities from atelectatic lung or pericardial sac to the chest wall. Three of the cases in the series presented this picture.

Subsequently, organization of the fibrinous adhesions occurred, probably with the absorption of varying amounts of fluid, and this process was sometimes encountered in all stages. A common picture was the combination of fibrin and loose fibrous tissue giving rise to fairly soft, white adhesions, which enclosed small, loculated areas of fluid, generally involving the medial, posterior and inferior surfaces of the lower lobes to a greater or less degree.

As with many inflammations of the pleura, eventually fibrous adhesions were left as landmarks of the previous lesion. The mere finding of such adhesions in our series of cases, of course, gave us little information as to their origin; we paid scant attention to them, therefore, apart from noting that they occurred in over 60 per cent of the cases. However, in none of these cases, which included many in which there had been a history of repeated attacks of rheumatic fever, did we find a really thickened or hyalinized pleura analogous to that of the older stages of tuberculous pleurisy.

Pleural Fluid: The type of effusion which has been so frequently encountered in the pleural cavities in the course of rheumatic fever has been described by Swift [5] and others.[6] In our series of cases, the pleural fluid varied in appearance from almost that of a transudate to that of a frank exudate, probably depending on the degree of inflammation of the pleura. As a rule, this fluid was straw colored, clear or slightly turbid; in a small number of instances, particularly in young children, it was definitely hemorrhagic. We have referred to the fact that the fibrinogen content was high. This was roughly demonstrated in the ability of the fluid to clot on standing. As a rule, however, fibrin showed itself by the presence of actual flecks or floating strings of white material, a glance at the open chest sometimes revealing the presence of small particles or, in some instances, huge masses floating or deposited on the pleural surfaces. As most of these particles were too large to penetrate the lumen of the ordinary trocar, they did not appear in the usual specimen obtained by aspiration. The cytologic content of the fluid was subject to great variations; we found, as a rule, however, a predominance of mesothelial cells and lymphocytes with a scarcity of polymorphonuclear cells.

In the many bacteriologic studies that we made, we failed to demonstrate bacteria in this fluid.

Histologic Studies of the Pleural Lesion: We confined our histologic studies to a few of the cases that we believed presented most characteristically the pleural inflammation peculiar to this disease. Here, again, the picture resembled that of rheumatic pericarditis. In the earlier stages, we found marked swelling and a uniform increase in the size of the lining mesothelial cells, so that they almost resembled columnar epithelium. One of the features of this metaplasia was the size and character assumed by the cell nucleus. It became large, pale and vesicular, almost foamy in texture, and was dotted with multiple, basophilic nucleoli (fig. 1). Scattered among these swollen cells were some showing

5. Swift, H. E.: Rheumatic Fever, Nelson's Loose-Leaf Living Medicine **1**:418, 1920.

6. Bezançon, F., and Weil, M. P.: La cortico-pleurite rhumatismale, Ann. de méd. **19**:184, 1926.

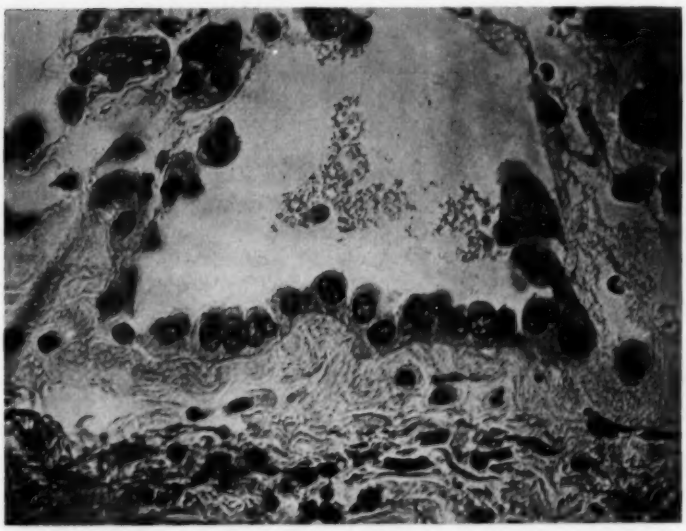

Fig. 1 (case 24).—A small portion of the pleural surface on which the lining endothelial cells show swelling and other characteristic changes. Many of them have formed multinucleated giant cells and have split away from the basement membrane.

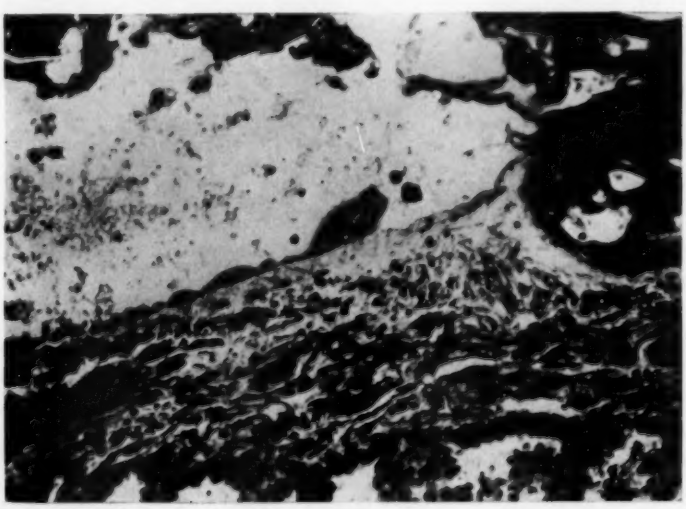

Fig. 2 (case 24).—A pleural surface showing endothelial swelling with formation of giant cells and desquamation. At the right, a mass of deeply stained fibrin covers the surface. Evidences of inflammation are present in the subpleural layers.

evidences of degeneration with vacuolization of the cytoplasm and shrinking and pyknosis of the nuclei, as well as some that showed nuclear division. Many of the cells became oval or spherical, forming large, multinuclear giant cells at this stage (fig. 2) and split away from their basement membrane (figs. 1 and 2), leaving a denuded surface, to which shreds of fibrin became attached (figs. 2 and 3). Associated with these changes of the lining mesothelium, particularly in the denuded areas, the subpleural tissues exhibited a low grade inflammatory reaction characterized by moderate edema and the appearance of scattered lymphoid cells, occasional polymorphonuclear cells, plasma cells, mast cells, eosinophils, etc. (fig. 3). It was not unusual to find in these areas large mononuclear cells in which the cytoplasm stained red with methyl-green-pyronin. New capillaries were formed in these subpleural areas. They often appeared as small ducts owing to the fact that their lining endothelium also sometimes showed varying degrees of swelling (fig. 3); occasionally they were thrombosed and sometimes showed hyalinization of their walls.

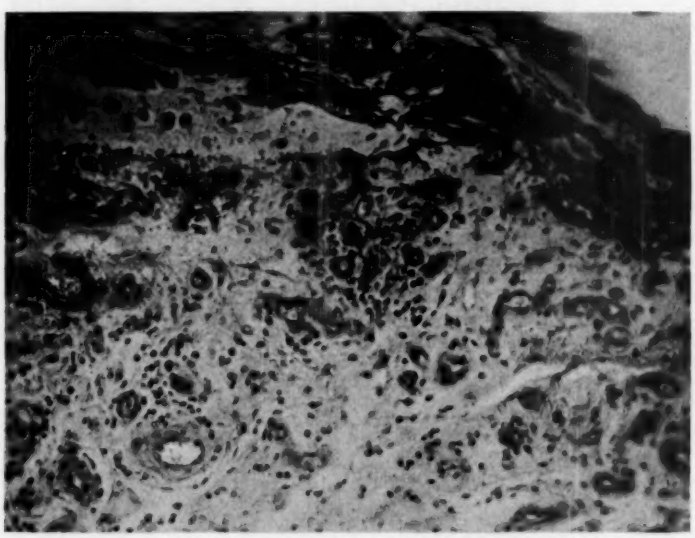

Fig. 3 (case 24).—A subpleural space. To the denuded surface, masses of fibrin have become attached, beneath which there is a wide layer of granulation tissue, rich in capillaries. Many of these show swelling of their lining endothelium, notably a vessel in the lower left hand corner. Scattered diffusely or in perivascular locations are many lymphoid, plasma and wandering cells.

The older pleural lesions gave rise to a variety of pictures. The subpleural spaces in some areas were replaced by a thick layer of granulation tissue, which was the site of an extensive inflammatory reaction. In other areas, in which moderate protection of the originally denuded surface had occurred, in the form of a thin hyalinized membrane probably derived from fibrin, the subpleural inflammatory changes were not nearly so pronounced. We sometimes found the surface in such an area thrown into folds, directly beneath which were fairly compact groups of large cells (fig. 4), recalling in some measure the histologic

picture of the now familiar lesion of the endocardium in the wall of the left auricle which was described by MacCallum [7] and von Glahn.[8]

Another striking picture which was noted in several cases with effusion was little, finger-like projections or mesothelium-lined villi on the pleural surface (fig. 5).

In general, however, neither the gross nor the histologic picture of this lesion was sufficiently specific to differentiate it clearly from that seen in a variety of types of pleural inflammation, except perhaps for the paucity of polymorphonuclear cells and the consistent absence of bacteria. Furthermore, apart from the fact that the injury appeared to be an acute or subacute inflammation, we know little of its true nature,

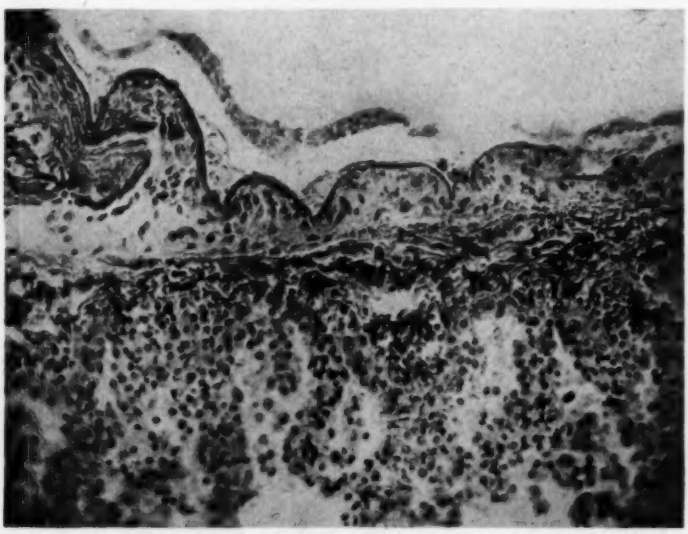

Fig. 4 (case 24).—A pleural surface from which the endothelial lining has desquamated and on which it has been replaced by a thin hyalinized membrane. A characteristic type of endothelial cell proliferation may be seen in the subpleural layers.

although we were impressed with the fact that one of its earliest demonstrable manifestations was in the lining mesothelium. The inflammatory processes which involved this mesothelium seemed to be essentially those of swelling, metaplasia, formation of giant cells, desquamation and cell death. Associated with this process, particularly after the pleural surface had been denuded of its lining, there was an intense,

7. MacCallum, W. G.: Rheumatic Lesions of the Left Auricle of the Heart, Bull. Johns Hopkins Hosp. **35**:324, 1924; Rheumatism, The Harrington Lecture, J. A. M. A. **84**: 1545 (May 23) 1925.

8. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, Am. J. Path. **2**:1, 1926.

rather characteristic chronic inflammation of the subpleural tissues and it is interesting to recall in this connection that French authors applied the term "cortico-pleurite" to rheumatic pleurisy in an endeavor to emphasize that there is a characteristic involvement of both the pleura and the subpleural layers. The growth of new capillaries into the subpleural space was marked, and they, too, presented swelling of the lining endothelium and also degenerative changes, such as hyalinization of their walls.

All these changes sometimes were and sometimes were not associated with underlying lesions in the lung proper. We were unable to assume that they represented the surface manifestations of a constant

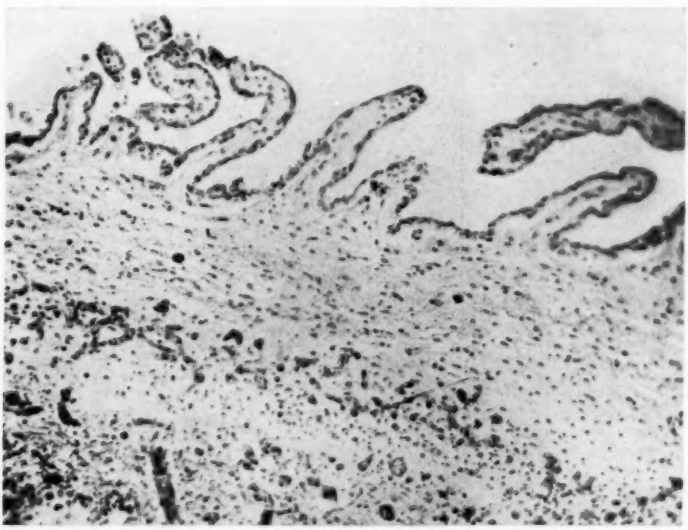

Fig. 5 (case 7).—Pleura and subpleural space. Endothelium lined villi project from the surface. Many new capillaries may be seen in the underlying spaces.

lesion within the lung. The phenomena reminded us rather of the pleural lesion of tuberculosis, which may or may not accompany an extensive intrapulmonic lesion.

Another question that concerns the nature of this pleural lesion and one which has been often raised is whether or not it represents an extension from the pericardial lesion. Many authors have called attention to the high incidence of pleural involvement in rheumatic pericarditis, although it has also been said that the pleurisy may develop without the carditis. In our series of cases, we observed four instances of active fibrinous pleurisy occurring in the absence of an active pericarditis. It was evident, none the less, that the pericardial and pleural lesions were

closely related by virtue of their proximity and by virtue of the fact that they appeared in the same general type of tissue; but, from the data at hand, we feel that the paths of infection cannot as yet be satisfactorily traced, for we do not know the nature of the infection. Nevertheless we are inclined to believe with Mosler [9] and others that serous surfaces are favorite sites of injury in rheumatic fever. Indeed, besides that of the synovial membranes, inflammation of the peritoneum and of the meninges has been noted. It is even conceivable that, in the thoracic cavity, one has an exaggerated local manifestation of a more generalized process for which local factors, such as the cardiac and respiratory movements, may be responsible—a possibility that is also reflected in the subdiaphragmatic peritonitis or perihepatitis to which attention has been called in this disease.

Vascular Lesions.—We reviewed the literature dealing with these lesions in a previous article.[1] It is interesting to compare our observations with those that have been recently described.

Main Pulmonary Artery: Atheroma of the pulmonary artery and its larger branches is a familiar observation in cases of long-standing pulmonary congestion, and especially in mitral stenosis. It was noted in two of our cases, in each of which both mitral and pulmonic endocarditis was present.

Histologic studies of the base of the main pulmonary artery were made in six cases. In one (table 1, no. 1), a case in which atheroma of the pulmonary artery had been noted grossly, microscopic lesions were found in the wall similar to those that have been described in the aorta in this disease.[3] The medial coat of the pulmonary artery was the seat of a destructive lesion, with splitting of the elastic fibers and an extensive deposition of scar tissue. Typical Aschoff bodies were also found in the adventitial layers of the base of the pulmonary artery and of the aorta.[10] (Kugel and Epstein [11] have recently reported the presence of similar lesions in five of a series of twenty-four active cases of rheumatic infections of the heart.)

Pulmonary Arteries of Moderate Size: Grossly, we were unable to detect any changes in these vessels other than occasional thrombosis. Histologically, fairly extensive changes were detected in four cases and slight changes in twelve others.

In the branches in which the lumen measures from 2 to 3 mm. in diameter, the lesion conformed rather with the type seen in the aorta or main pulmonary artery. The histologic picture was not striking, consisting, as it did, of slight metaplasia or proliferation of intimal cells together with thickening of the medial coat. Furthermore, it did not seem to be particularly specific, recalling

9. Mosler, E.: Ueber rheumatische Entzündung der serösen Häute (sogenannte Polyserositis rheumatica), Berl. klin. Wchnschr. **47**:277, 1910.

10. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, Tr. Path. Soc., Philadelphia, Arch. Path. **3**:352 (Feb.) 1927.

11. Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, Arch. Path. **6**:247 (Aug.) 1928.

the changes that have been described as occurring in the peripheral blood vessels in a variety of acute infections,[12] such as influenza, etc.

Arterioles: The lesions in the arterioles appeared to be the most prominent, although it may have been only because the changes in the arterioles were more easily detected than those in vessels of larger caliber. This was particularly true of vessels in which the lumen was about the size of a glomerulus. As a rule, we found either many vessels involved or none at all, and such changes, both recent and old, were found in about 40 per cent of our cases. Focal hemorrhages within the lung or hemorrhagic bronchopneumonia invariably accompanied this lesion. Histologically, the process was well described by von Glahn and Pappenheimer (1926).[3] It seemed to be essentially a panarteritis, although the most striking changes manifested themselves in the intima and the adventitia. Primarily, the lining endothelium became swollen and vacuolated, so that the intima often

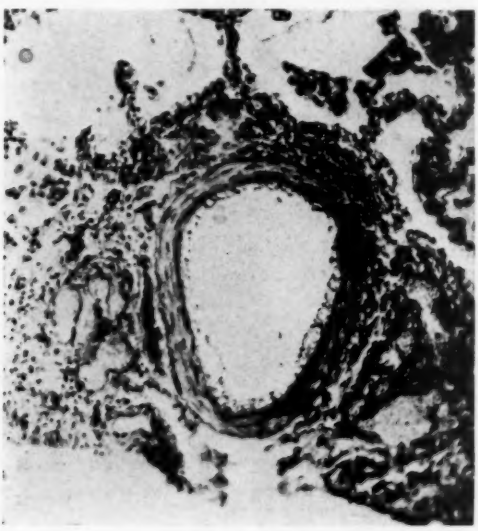

Fig. 6 (case 23).—A small pulmonary artery. The intimal cells are vacuolated and raised away from the elastic membrane. There is marked congestion of the perivascular vessels, with some perivascular accumulations of cells.

appeared raised away from its basement membrane by delicate strands (figs. 6 and 7). A more pronounced and perhaps a later stage of this process was the formation on the intimal surface of a layer of foamy or vacuolated cells. In the media, we sometimes also found vacuoles associated with distortion of the muscle fibers and accompanying evidences of injury and death of cells, as shown by the presence of pyknotic and shrunken nuclei. Associated with the early stage of intimal metaplasia and proliferation there was sometimes, in the adventitia or in a perivascular zone, a corresponding response to damage of the tissue, characterized by marked dilatation and hyperemia of the perivascular capillaries (fig. 6). Accompanying this hyperemia were other evidences of local

12. Wiesel, J., and Löwy, R.: Die Erkrankungen der peripheren Gefässe bei akuter und chronischer Krieslauf insuffizienze, Wien. klin. Wchnschr. **32**:1083, 1919.

injury, such as hemorrhage and the presence of fibrin and a few scattered wandering cells. However, such perivascular accumulations of wandering cells were not, as a rule, extensive in actual numbers of cells. In character, they recalled, for the most part, those which we described as occurring in association with the pleural lesion; rarely did we see many polymorphonuclear cells; occasionally, we found cells in this location in which the cytoplasm stained red with the Unna-Pappenheim stain, but we failed to find groups of cells that recalled the classic Aschoff nodule of the myocardium. The occurrence of thrombi within the lumina of injured vessels was frequently noted. Frank obliterative endarteritis was also noted, but it was generally found with some other lesion of the lung, such as atelectasis, which might well be responsible for involutionary changes in the vessels.

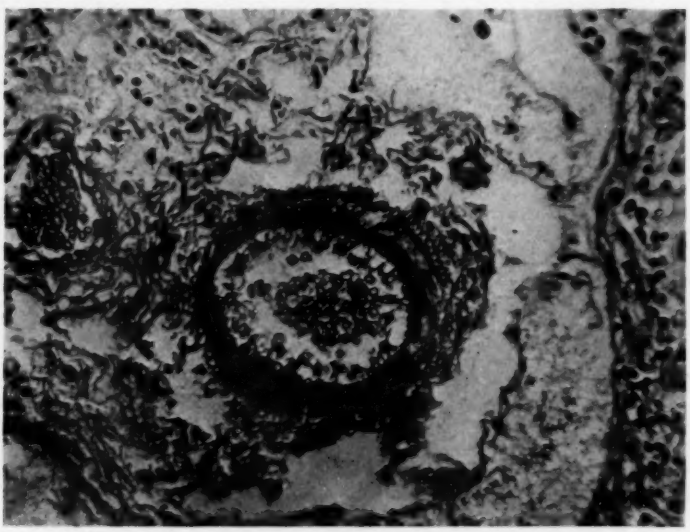

Fig. 7 (case 23).—A pulmonary arteriole with intimal changes.

Reparative or end-stages of the vascular lesions were manifested by slight thickening and hyalinization of the intima and thickening and scarring of the medial coat, together with perivascular fibrosis.

Veins: We did not detect any noteworthy changes in the walls of the veins.

Other lesions involving the lung proper which were encountered may be listed as follows:

Pulmonary Atelectasis.—Although varying in degree, this was an almost constant observation in the dependent portions of the lung, particularly of the left lung. A number of factors probably played a rôle in bringing about this phenomenon, such as fluid in the pleural cavities; the enlarged pericardial sac generally associated with pericarditis, and bronchitis, which may inhibit pulmonary aeration. Pericardial enlargement, however, proved to be a particularly important contributing factor.

We cannot overemphasize the relatively enormous size which the pericardium sometimes attained in these cases, due either to cardiac enlargement, to an effusion or to fibrinous pericarditis with associated edema of the sac wall, to an old obliterative pericarditis or to a combination of some of these processes. Pulmonary compression from enlargement of the pericardial sac was present in at least two thirds of the cases.

Histologically, the changes in the atelectatic areas did not prove to be remarkable, except that in the pulmonary vessels in certain lungs which had undergone long-standing compression, the degree of endarteritis was sometimes extreme, often resulting in a marked diminution of the lumen. We also found various stages of perivascular inflammation and fibrosis. We believe that such changes were distinct from the specific vascular changes described and that they were essentially involutionary as a result of prolonged pulmonary compression. In the atelectatic areas, the bronchi also became, at times, the seat of an intense chronic inflammatory reaction.

Bronchopneumonia or Lobular Pneumonia.—Considerable discussion has arisen as to whether a specific type of pneumonia exists in rheumatic fever.[13] One of the difficulties in reaching an agreement seems to be that of terminology or definition. In our series, examples of the classic bronchopneumonia occurring in a variety of acute infections, such as measles and influenza, appeared to be relatively uncommon, but a rather unusual hemorrhagic lesion that may be logically classed as a "pneumonia" seemed to be not at all infrequent. This latter lesion was represented by multiple hemorrhagic foci sometimes widely scattered throughout the lung substance. It was a particularly common observation in fatal cases in children, and has been described, according to Naish,[4] by Pichon and Lardé-Arthés.

> In this condition, the pleural surfaces presented a mottled appearance due to small, generally round and definitely firm areas of subpleural hemorrhage, averaging from 0.5 to 1.5 cm. in diameter, and limited, as a rule, to individual lobules (fig. 8). Similar hemorrhagic foci, more or less lobular in distribution, were also found scattered throughout the lung substance as round, dark red nodules.
>
> Histologically, these small hemorrhagic areas appeared as compact masses of red cells and fibrin within individual alveoli and atriae (fig. 9). A small portion of a lobule, a whole lobule or several lobules were occasionally involved, but, as a rule, the areas were focal rather than confluent. The picture suggested actual intra-alveolar hemorrhage and one of the outstanding characteristics of the material that collected in the alveoli was the amount of fibrin, so that in late stages, as the result of its organization, groups of alveoli and even bronchioles became filled with a cast of loose fibrous tissue. We studied these areas of focal hemorrhage with bacterial stains, and in none of them were we able to demon-

13. Rabinowitz, M. A.: Rheumatic Pneumonia, J. A. M. A. **87**:142 (July 17) 1926.

strate bacteria in the interstitial tissue or within the alveoli. In practically all the cases, however, moderate degrees of bronchitis or bronchiolitis were present and bacteria were easily demonstrable within the lumina of terminal bronchi, associated with definite inflammation of the mucous and submucous coats.[14]

Associated with this hemorrhagic lesion and probably representing a later stage, intra-alveolar exudate, fairly rich in polymorphonuclear cells, was found in four of the cases. The picture was characterized grossly by patches of confluent lobules showing gray hepatization. Here, again, however, we experienced difficulty in demonstrating bacteria and in only one did we succeed in demonstrating them within the alveoli; the age of the process, however, may have been responsible for their absence.

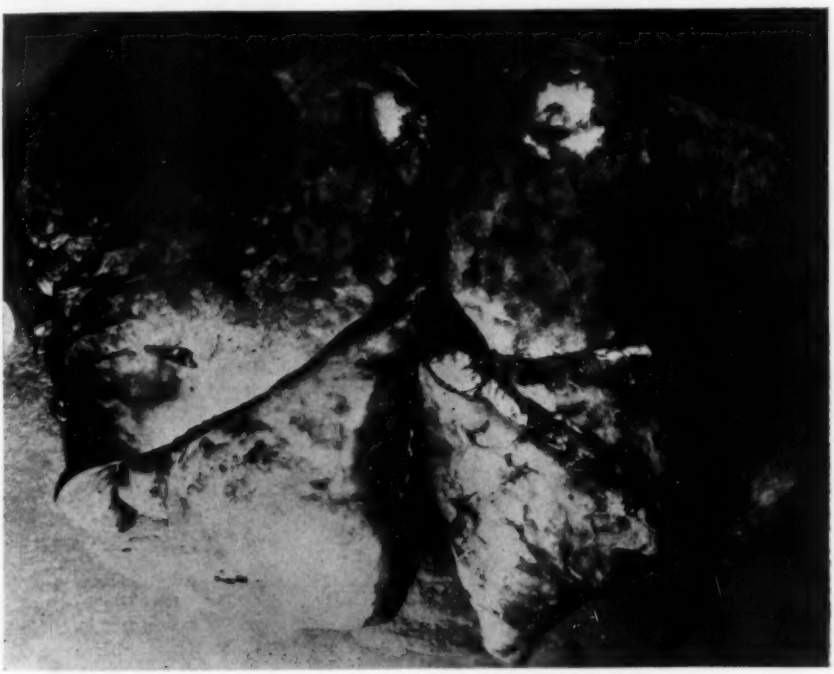

Fig. 8 (case 26).—The lungs viewed posteriorly. Hemorrhagic foci are well shown in the upper lobes and their relationship to individual lobules can also be discerned.

Although the nature of this characteristic lesion was not clear, the picture suggested that of an acute hemorrhagic lobular pneumonia. A

14. Cultures were taken from four of the lungs showing the hemorrhagic lesions. From one of these, we did not obtain any growth at all; from two, we obtained small numbers of Streptococcus viridans and from another a scanty growth of anhemolytic streptococci. We have not stressed the significance of these results, for we do not know whether the organisms were actually obtained from the lung tissue proper or from the lumen of a terminal bronchiole. However, the bacteriologic observations were not quite in accord with those usually encountered in hemorrhagic lobular pneumonia.

number of factors, however, may have influenced this picture; the lesion may have been the result of an injury to the vessel walls, such as the lesions just described, or it may have been the result of a pneumonia in a lung that was already the seat of marked circulatory stasis.

Bronchitis and Bronchiolitis.—Bronchitis or bronchiolitis was an almost constant observation, associated, no doubt, with the ever present circulatory stasis.

Chronic Passive Congestion.—Pulmonary congestion was present in some degree in every case. Nothing particularly remarkable was noted about this picture except perhaps the fact that frank pulmonary edema was uncommon. Most of the lungs were "dry" rather than

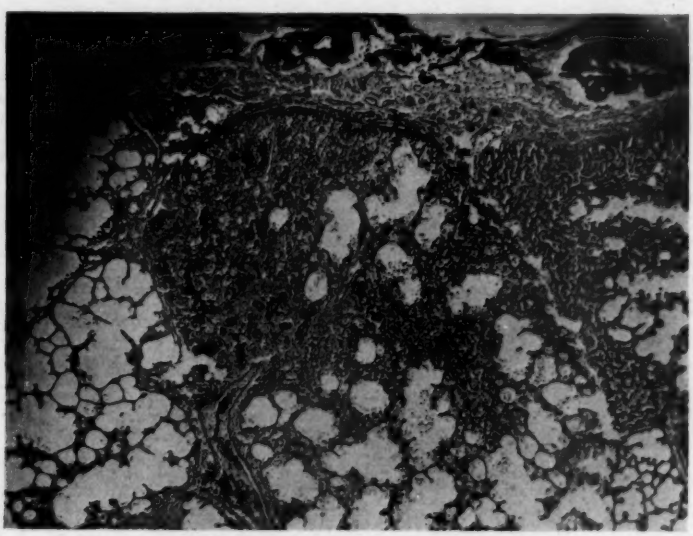

Fig. 9 (case 24).—A typical histologic view of the hemorrhagic lesion shown grossly in figure 8, including a peripheral lobule and the adjacent pleura. One may note the lobular distribution of the exudate, which consists largely of red cells.

"wet." The picture was often complicated by varying degrees of pulmonary atelectasis in the dependent parts of the lungs.

Thrombosis of Pulmonary Arteries and Pulmonary Infarction.—Thrombi were found in pulmonary arteries of considerable size with relative frequency, occurring in several instances without the presence of infarcts. Gross pulmonary infarcts were present in six cases, or 20 per cent of the series. In five of these cases, pulmonary infarction was associated with the accumulation of an excess of fluid in the pleural cavity on the affected side.

Summary of Observations.—The observations in the series have been summarized in the accompanying table, in which the cases have been ranged according to the ages of the patients. The cardiac lesions are also tabulated in a way to show the degree of myocardial, endocardial and pericardial involvement. The close association between fibrinous pericarditis and fibrinous pleurisy is shown by this table. The cases showing hemorrhagic lobular pneumonia have been listed in a separate column. It may be noted that this lesion is sharply restricted to patients under 20 years of age.

Cardiac and Pulmonary Lesions Encountered in the Series of Cases of Fatal Rheumatic Fever

		Cardiac Lesions						Pulmonary Lesions					
		Myocarditis—Aschoff Bodies	Endocarditis¶			Fibrinous Pericarditis	Fibrinous Pleurisy	Pleural Fluid, Cc.		Vascular Lesions	Hemorrhagic Foci	Bronchopneumonia with Gray Hepatization	Gross Infarcts
Case*	Age		T	P	M	A			Right	Left				
24	6	+++†	+	..	+	+	+++	+++	0	0	+++	+++	0	0
6	8	+	..	..	+	+	+++	++	150	50	0	++	+	0
16	10	++	..	..	+	+	+++	+	300	300	0	+	0	0
4	13	++	+	..	+	+	+++	±	600	30	0	+	±	0
15	14	++	..	..	+	+	++	+	0	0	0	+	0	0
21	14	+++	+	..	+	+	±	0	50	50	+ (old)	+	0	0
26	14	0	..	..	+	+	0	+	50	50	0	++	0	0
27	14	±	+	..	+	+	0	+++	2,000	200	±	±	±	++
19	15	±	..	..	+	+	0	±	75	100	0	+	0	0
22	15	+	+	..	+	+	+++	++	500	800	±	+	0	+
23	15	++	..	..	+	+	0	+	0	0	++	++	0	0
5	16	++	..	..	+	+	+++	++	0	200	± (old)	+	+	0
10	16	+	..	..	+	+	+++	++	200	200	0	+	0	0
11	16	0	..	..	+	+	+++	+	50	20	+ (old)	0	0	0
9	17	+	+	..	+	..	++	+++	1,800	100	0 (old)	+	0	++
2	19	0	+	..	+	+	±	0	1,000	250	+ (old)	+	0	+++
7	19	+++	..	..	+	+	+++	++	200	20	+	++	0	0
20	19	+	+	..	+	+	+	+	250	150	+ (old)	++	+	0
28	21	+++	+	+	+	+	+	0	200	150	+ (old)	++	±	0
12	22	±	+	..	+	+	+++	±	200	0	+ (old)	0	++	0
17	22	++	..	..	+	+	+++	+	200	200	+ (old)	0	0	0
8	23	±	+	+	+	+	+++	+	600	0	0	0	0	0
14	24	0	..	..	+	+	0	+	500	75	0	0	0	0
18	24	+++	+	+	+	+	+	+	1,500	800	±	0	0	+
13	25	±	+	..	+	..	+	0	0	0	±	0	0	+
25	25	+	+	..	+	+	+	±	200	20	(old)	0	0	0
3	28	±	+	+	+	+	+	+	400	100	+ (old)	0	0	0
1	32	+++	+	..	+	..	+	0	1,000	0	0	0	0	0

* The cases are ranged in order of the ages of the patients.
† The most extensive lesions are designated as +++.
¶ T P M A indicate tricuspid, pulmonic, mitral and aortic valves.

CONCLUSIONS

We have listed the pleural and pulmonary observations in a series of twenty-eight necropsies performed on patients dying in active stages of rheumatic fever.

Primarily, we have been impressed with the relative frequency of pleurisy in this series, active inflammation of the pleura having been detected in about half the cases. Although difficult to define, the pleurisy described represents, we believe, a specific manifestation of the rheumatic infection and is distinguishable from that encountered in the

usual bacterial infections of the respiratory tract by the nonsuppurative character of the exudate and by our inability to demonstrate bacteria in association with it. This lesion, which resembles rheumatic pericarditis, is probably more common than is generally thought to be the case. It is, as a rule, less extensive than pericarditis, and associated with far less serious consequences. It manifests itself in a number of different forms but is generally accompanied by the accumulation of pleural fluid, which may be hemorrhagic, particularly in young children, and is nearly always rich in fibrin. It bears a close resemblance to tuberculous lesions of the pleura, but differs from this last infection in that it does not reveal a thickened, hyalinized pleura as an end-stage.

We have also studied the lesions that occur in and about the pulmonary vessels, and in this study have confirmed the observations of von Glahn and Pappenheimer (1926).[3] Rheumatic fever is not the only disease that gives rise to changes of this general type, particularly in peripheral vessels, for we recognize the arteritis of several acute infections. Nevertheless, we are impressed with the fact that such lesions are prominent in rheumatic fever and that they appear to be manifestations of a generalized infectious process.

Terminal lobular pneumonia, in its ordinarily accepted sense or in the sense in which it occurs following measles or influenza, proved to be fairly uncommon in our series, but we noted, particularly in those cases occurring in childhood, the presence of focal or hemorrhagic lobular pneumonia exhibiting certain atypical features as described. Evidence has not accumulated to suggest that this lesion is a specific manifestation of rheumatic fever, although it seems to be a fairly constant observation in the disease.

CONGENITAL STENOSIS OF THE THIRD PORTION OF THE DUODENUM WITH ACUTE OCCLUSION AND RUPTURE OF STOMACH *

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AND
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The case here reported is of interest from a clinical as well as from a pathologic point of view: from the former, in that the patient had had, throughout life, symptoms of intermittent high intestinal obstruction, which led finally by acute occlusion and rupture of the stomach to death; and from the latter, in that the occlusion was in the inferior horizontal portion of the duodenum exactly at the site where arteriomesenteric occlusion of the duodenum occurs. In fact, the condition was at first regarded as such; closer examination, however, revealed a marked stenosis of the duodenum, the lumen being partially occluded by a membranous septum with an opening about 4 mm. in diameter. The wall of the duodenum oral to the site of obstruction was distinctly hypertrophied, as was also the wall of the stomach. The rupture of the stomach was on the anterior wall near the cardia and was presumably the result of overdistention from the injudicious administration of enemas. The combination of unusual features makes this case unique.

REPORT OF CASE

Clinical History.—The patient was a girl 8 years of age. The father stated that she had had attacks of nausea and vomiting, abdominal distention, pain in the upper part of the abdomen and constipation for several years. At times, the child would vomit material which had been eaten days or even weeks before. Enemas usually gave relief. On March 8, 1928, the child ate a lunch consisting mainly of a thick vegetable soup of cabbage, corn and spinach. At about 4 p. m. she complained of abdominal distention and pain. The mother then gave her an enema of soap suds and castor oil by the gravity method. None of the first enema was returned; so a second, third and fourth were given, with apparently no appreciable amount of fluid being returned in any instance. An enema bag of 2-quart size was used; conservatively, from 4 to 6 quarts of fluid were probably injected. The patient commenced vomiting a greenish fluid. Her condition became rapidly worse. A physician was called and the child was removed to the South Shore Hospital. By this time there was extreme cyanosis; the abdomen was greatly distended, tympanitic and of boardlike rigidity. A diagnosis of pneumoperitoneum was made. At 8:30 p. m., while being prepared for operation, the patient expired.

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* Submitted for publication, April 8, 1929.
* From the Department of Pathology, University of Chicago.
* Read at the Chicago Pathological Society, April 9, 1928.

Necropsy.—The postmortem examination was made one hour later. The child was well developed and well nourished. Rigor mortis was not present. Cyanosis was extremely marked. The abdomen was tremendously distended and tympanitic, and when it was opened, air under great pressure escaped. The abdominal cavity contained approximately 1.5 liters of a soapy, oily fluid, together with cabbage and spinach leaves and fragments of corn. Smears from this revealed only yeasts and a few gram-positive cocci. At a point from 1 to 2 cm. from the cardiac orifice of the stomach was a tear about 1.5 cm. in diameter, through which vegetable leaves protruded. The stomach was markedly distended by a soapy, oily fluid, and contained vegetable leaves and débris, six olive seeds and two glass beads.

Fig. 1.—The abdominal viscera after the small and large intestines were inflated with air through a cannula inserted into the rectum.

To the left of the esophageal hiatus and extending into the mediastinum was a hernia-like pouch into which vegetable leaves were packed.

The doudenum was greatly dilated and the wall distinctly thickened to a point where the mesentery crossed the inferior horizontal portion. From here on, the small intestine and colon were relatively collapsed and free from fluid. A noteworthy feature was the presence of countless air bubbles between the layers of the mesentery, particularly of the mesocolon and mesosigmoid. The intestines contained practically no fecal material. Air introduced into the rectum by a tube, passed easily throughout the bowel up to the place where the obstruction occurred (figs. 1 and 2). When the mesentery was lifted, the air passed into the remainder of the duodenum.

The other significant observations were: marked distention of the right side of the heart with dark blood, small ecchymoses in the pleurae of both lungs and acute generalized passive hyperemia.

Description of Fixed Specimen.—The specimen, as shown in figures 1 and 2, consisted of all the abdominal organs removed and fixed in toto.

The stomach was distended and, except for a tear near the cardiac orifice, presented nothing unusual on external examination. There was a slight narrow-

Fig. 2.—The abdominal viscera showing the enlargement of the duodenum.

ing corresponding to the pyloric ring. The duodenum was immensely dilated and its wall appeared firm. The dilatation extended up to a point where the inferior horizontal portion of the duodenum was crossed by the root of the mesentery; beyond this point, the duodenum, as well as the jejunum and ileum, appeared normal. The stomach and duodenum were opened by scissors, the former on the ventral surface about 3 cm. from and parallel to the greater curvature, the latter along its convex margin. In the fornix of the stomach, the plicae were scarce;

in the corpus, they were less prominent than is usual. The following measurements were taken: the wall was 2 mm. thick about the fornix, from 3 to 6 mm. in the prepyloric region and 8 mm. thick 1 cm. oral to the pyloric ring. The circumference of the stomach, 5 cm. oral to the pyloric ring, was 13 cm.; at the pyloric ring, it was 4.5 cm.

The wall of the duodenum was thickened and its mucosa appeared to be stretched. Three centimeters distal to the pyloric ring, the circumference of the duodenum was 11.5 cm., and the wall was 2 mm. thick. An iris-like membranous diaphragm narrowed the lumen of the duodenum at a point 18 cm. from the

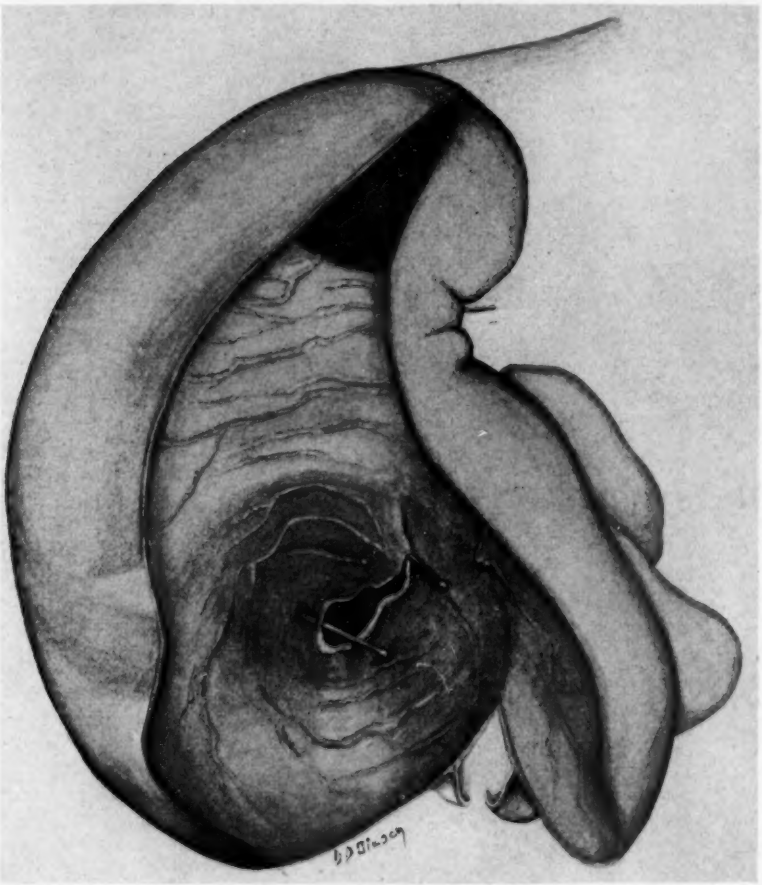

Fig. 3.—View of the concave (oral) surface of the iris-like septum narrowing the lumen of the duodenum (schematic drawing). The duodenum is opened along its convex margin, permitting a view of the oral, concave surface of the membranous septum. The opening in the septum has the shape of a reversed comma, with the head to the right and the tail to the left. The probes inserted mark the entrance of the ductus choledochus (head of the comma) and the ductus pancreaticus (tail of the comma), respectively.

pyloric ring measured on the convex margin and 8 cm. on the concave margin. One centimeter proximal to this diaphragm, the duodenum measured 15 cm. in circumference. This membranous diaphragm was dome-shaped with the peak

directed aborally, and measured 4 cm. in the ventrodorsal and 3 cm. in the transverse diameter. It had an eccentrically situated orifice about 4 mm. in diameter. On the oral, concave surface, the opening had the shape of a reversed comma, 25 mm. long, with the head to the right and the tail to the left (fig. 3). On the aboral, convex surface, the opening corresponded to the head of the comma and was situated at the dorsal end of the ventrodorsal diameter (fig. 4). The common bile duct opened in the free margin of this diaphragm. The pancreatic duct entered at the medial or tail end of the comma on the oral surface of the diaphragm.

On the external surface of the duodenum corresponding to the attachment of this membranous diaphragm there was a slight groove. A distinct narrowing of the bowel was noted at the point where the root of the mesentery crosses the inferior horizontal portion of the duodenum. Here the bowel measured 3.5 cm. in circumference, whereas, 1 cm. proximal to this point, the circumference was

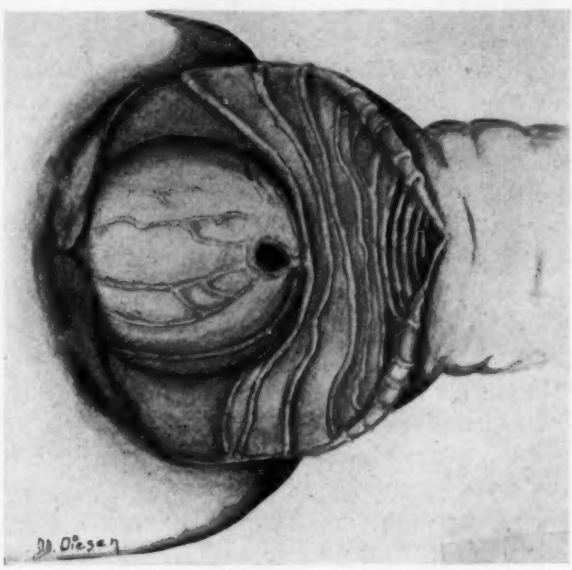

Fig. 4.—View of the convex (aboral) surface of the iris-like septum narrowing the lumen of the duodenum (schematic drawing). The duodenum is opened from the point of attachment to the membranous septum, along the free margin, permitting a view of the aboral, convex surface of the septum. The opening in this septum is eccentrically situated, measures about 4 mm. in diameter and corresponds to the head of the comma on the concave surface.

6 cm. In the portion of the duodenum aboral but adjacent to the membranous diaphragm, the folds of the mucosa were low and few in number. It appeared as if the dome of this diaphragm had pressed on the adjacent portion of the bowel wall "ironing out" the folds. The peak of the dome ended at the point where the root of the mesentery crosses the inferior horizontal portion of the duodenum.

COMMENT

The type of malformation of the duodenum in which the lumen of the intestine is narrowed or completely occluded at about the level of the

papilla of Vater is extremely rare. An analysis of the clinical course and observations at necropsy of the cases, records of which were available to us, reveal that these readily fall into three groups:

In the first, the membranous obstruction of the duodenum is complete, and death occurs soon after birth. The cases presented by Champneys and Power,[1] Wyss,[2] Roe and Shaw [3] (reported also by Keith [4] and Spriggs [5]) and by Weber [6] may be cited as examples.

1. Champneys and Power (1897) found at necropsy of a child, 5 days old, "that the lumen of the intestine was completely interrupted by a septum stretching across it at a point immediately upon the gastric side of the middle of the second part of the duodenum." The common bile duct entered the intestine just beyond the septum.

2. Wyss (1900) described a specimen in the pathologic anatomic collection of the Children's Hospital in Zürich, obtained in 1884, from a male infant 1½ days old. The lumen of the duodenum was divided by a membranous septum situated just above the level of the opening of the common bile duct. There was no opening in the membrane, which was 0.4 mm. thick in the center and about 0.5 mm. thick at the periphery. The circumference of the duodenum at the level of the membrane was 3 cm.; 5 cm. aborally, the circumference was 2 cm.

3. In a male infant who died suddenly on the fifth day after birth, Roe and Shaw (1911) found at necropsy a septum completely occluding the lumen of the duodenum immediately above the entrance of the common bile duct.

4. In Weber's case (1910), the female infant died on the tenth day after birth. At necropsy, a membrane was discovered stretching across the lumen of the duodenum below the level of the papilla of Vater, completely occluding the lumen of the intestine.

5. Another most peculiar case of this type was described by Keith (1910). The specimen (in the museum of St. Bartholomew's Hospital, presented by M. T. Harrison) is "from an infant aged 9 months, who had been subject during life to recurring attacks of vomiting. The vomitus was abundant, the attacks occurring at intervals of some days.

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1. Champneys, F. H., and Power, D'Arcy: Occlusion of the Duodenum by a Complete Transverse Septum, Brit. M. J. **1**:718, 1897.

2. Wyss, M. O.: Ueber kongenitale Duodenal-Atresien, Beitr. z. klin. Chir. **26**:631, 1900.

3. Roe, W. F., and Shaw, E. H.: A Case of Congenital Atresia of the Duodenum, Lancet **2**:947, 1911.

4. Keith, A.: Constrictions and Occlusions of the Alimentary Tract of Congenital or Obscure Origin, Brit. M. J. **1**:301, 1910.

5. Spriggs, N. J.: Congenital Intestinal Occlusion, Guy's Hosp. Rep. **66**:143, 1912.

6. Weber, W.: Zur Kasuistik der angeborenen Atresie des Duodenums, Med. Klin. **6**:1294 and 1334, 1910.

There had never been a normal evacuation of the bowels, the motions being constituted by small spherical masses of faeces." A diaphragm with no evidence of an orifice "though the history of the case proves that some opening must have existed" occluded the lumen of the duodenum at about the level of the papilla of Vater. The fact that there was no record of bile having been vomited and that the bowel below the septum had a fair sized lumen supports the idea that the bile duct discharged its content below the septum, although an opening could not actually be detected in the specimen.

In the second group of these cases, the membranous obstruction of the duodenum is incomplete in that a small opening permits the passage of liquids. Trouble usually starts with the change to more solid foods. As far as we could determine, only two cases of this kind have been reported: one by Buchanan,[7] the other by Seidlin.[8]

1. Buchanan presented to the Pathological Society of London in 1861 the case of a female child, 18 months of age, who was apparently in good health until about five weeks before death; then she started vomiting and rejected everything she ate. Although vomiting had ceased two weeks before death, the postmortem appearances of the organs led to the conclusion that death was due to starvation. The necropsy disclosed "a septum stretched transversely across the calibre of the bowel" with a hole, 2.5 mm. in diameter, in the center. The septum measured about 20 mm. from the attached border to the rim of the opening. "Held up to the light," the septum showed two darker streaks traversing it from the periphery to the center: the ductus choledochus, which entered the intestine at the hole below the septum, and the pancreatic duct, which opened at the upper surface of the septum. The history being incomplete, Buchanan stated that "it is likely that while the child was at the breast, the scanty residuum of its food found no difficulty in passing the orifice of the duodenal septum, and any inconvenience was probably postponed during the time that the child, after weaning, was fed on a milk diet. Vomiting may be believed to have begun when more solid food—perhaps of an indigestible kind—was presented to the stomach, and conversely, a return to spoon food, when the child was considered an invalid, may have been the reason of the cessation of the vomiting."

2. Seidlin's case (1925) concerned a colored girl, 2½ years old, who was breast fed until 14 months of age. From the fourteenth to the eighteenth month the child continued nursing, with the addition of whole cow's milk, cereals and orange juice. From then on, the diet consisted of milk, cereals, vegetables, fruits and meats. She had always been sub-

7. Buchanan, George: Malformation of the Duodenum in a Child, Tr. Path. Soc. London **12**:121, 1861.

8. Seidlin, S. M.: Congenital Duodenal Septum with Obstruction, Bull. Johns Hopkins Hosp. **37**:328, 1925.

ject to constipation, but seemed to develop normally. Her trouble began three days before admission to the hospital. The only unusual item in her diet had been some canned corn, which she had eaten about two weeks before. Her mother noted that the child's abdomen had increased in size and seemed "knotted up." The following day, the child vomited several times and continued to vomit everything that was given to her, complained of abdominal pain and, for three days, retained no food. Some kernels of corn were discovered in the vomitus. During the first five days in the hospital, she was kept on a diet of milk and soft foods; she gained weight and seemed in no discomfort. She was then given a regular diet. That evening the abdomen became distended, and large peristaltic waves were noted in the upper part of the abdomen. She was again put on a diet of soft food, but the next day her appetite was poor and she vomited once. Milk was then given as the only food, but she continued to be weak and listless, developed a subnormal temperature and died on the eighth day after admission.

At necropsy, the duodenum was found to be occluded by an iris-like septum stretched across the lumen about 10 cm. above the duodenojejunal junction, measured along the concave margin of the duodenum. The portion of the duodenum above the septum was larger than the portion below, and its wall was considerably thickened. The septum was dome-shaped, with the convexity directed aborally. "In its most convex portion there was an eccentrically placed opening, about 7 mm. in diameter, situated somewhat posteriorly and cephalad to the center of the septum." The lumen of the opening was completely plugged with semisolid, stringy food material. On the oral side of this plug there were several kernels of corn and one bean. The common bile duct opened into the lumen of the duodenum on the aboral surface of the septum close to the margin of the septal opening after a course in the wall of the septum. The pancreatic duct passed also into the septum and opened on the oral surface of the latter at a point midway between the posterior margin of the septum and its central orifice.

In the third group of these cases, the membranous obstruction is so incomplete that from it little or no distress results during life, and the condition is usually discovered at necropsy as an incidental feature. Examples are those described by Silcock,[9] Keith,[4] and Nagel.[10]

1. In the case reported by Silcock (1885), the patient, a woman, aged 34, died of a generalized peritonitis secondary to a perforated intestinal ulcer. During the necropsy, a "congenital septum" was discov-

9. Silcock, A. Q.: Epithelioma of Ascending Colon; Enterocolitis; Congenital Duodenal Septum, with Internal Diverticulum, Tr. Path. Soc. London **36**:207, 1885.

10. Nagel, G. W.: Unusual Conditions in the Duodenum and Their Significance, Arch. Surg. **11**:529 (Oct.) 1925.

ered in the duodenum "six inches below the pylorus" with a lumen barely admitting "the tip of the little finger," which apparently had caused no symptoms during life.

2. Keith (1910) described a specimen found in the collection of St. Mary's Hospital Medical School, as follows: "The dilated duodenum of an adult is crossed by a diaphragm above the opening of the common bile duct. In the diaphragm, which is ballooned downwards into the second stage of the duodenum, there is an oval orifice measuring about 5 by 3 mm."

3. Nagel (1925) reported the case of a man, aged 72, who died of pulmonary embolism after a laparotomy. At necropsy, the lumen of the duodenum was partially occluded by a transverse septum, located 1.5 cm. above the papilla of Vater. This septum was slightly concave above, was 5 mm. thick at its attachment and tapered down toward the center, where eccentrically placed, was an oval opening 8 mm. in its greatest diameter. The symptoms during life were attributed to a pseudodiaphragmatic hernia about the hiatus oesophageus, discovered at operation. This, however, as Nagel remarked, could scarcely have been "a factor in the cause; it was probably a result of hyperperistalsis with dilatation of the oesophagus and stretching of its diaphragmatic hiatus."

In this group belong, perhaps, those cases in which one of the folds normally present in the pars descendens of the duodenum attains an unusual height, thereby narrowing the lumen of the bowel considerably. One of us [11] has called attention to the fact that frequently no circular plicae of any prominence are seen in the middle third of the pars descendens duodeni, the fold immediately above the plica longitudinalis and the first fold below the opening of the papilla being more prominent than any of the others (fig. 5).

Our case appears to belong rather to the second than to the third group. The duodenum was partially obstructed, permitting the passage of certain solid foods, but as the result of mechanical plugging, it was probably completely occluded at times. This condition was aggravated because increased intraduodenal pressure caused the septum to bulge toward the area where the crossing of the mesentery could offer an added hindrance to the free passage of the duodenal contents.

The rupture of the stomach is also of unusual interest. There is no doubt that most of the fluid used in the enemas traversed the intestine and entered the stomach with a resulting overdistention of the latter. Dragstedt [12] demonstrated that fluid introduced into the rectum of a dog, under a hydrostatic pressure of 150 cm., will traverse the entire bowel

11. Halpert, Béla: The Arrangement of Folds in the Pars Descendens Duodeni, with Special Reference to Their Relationship to the Papilla of Vater, Anat. Rec. **32**:232, 1926.

12. Dragstedt, C. A.: Personal communication.

and cause great overdistention of the stomach and death of the animal within from eighteen to twenty-four hours. In our patient, the hypertrophied wall of the stomach may have caused more powerful contractions; these and the other forces concerned in the act of vomiting probably induced the rupture near the site of transition of the esophagus to the stomach.

A survey of the available literature of the past ten years reveals only three instances of rupture of the apparently normal stomach from overdistention, and none associated with stenosis of the duodenum.

Busch [13] summarized the literature on this subject to 1924 and reported one case, in which the rupture occurred following great overdistention from the excessive intake of food. From this and the previously reported cases, Busch concluded that rupture of the normal

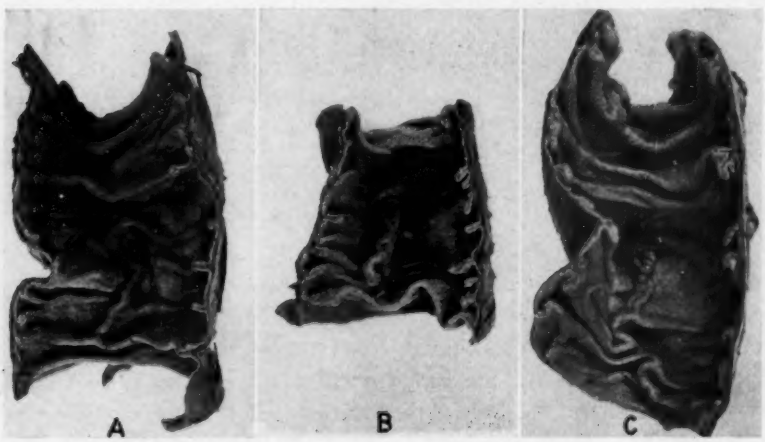

Fig. 5.—Photographs of the region of the papilla of Vater showing that the middle third of the pars descendens duodeni is void of circular plicae of any prominence, the fold above and the first circular fold below the opening of the papilla being more prominent than any of the others. A noteworthy feature in all three of these is the presence of a plica longitudinalis infrapapillaris which has nothing to do with the plica longitudinalis suprapapillaris (present only in fig. 5 *A*), a fold indicating the course of the intramural portion of the ductus choledochus.

stomach is an extremely rare condition and arises only in the course of an acute dilatation of the stomach. The usual place of rupture in the cases reported was in the lesser curvature near the cardia.

More recently, Murdfield [14] reported the case of a man, aged 39, who attended a feast and drank unusual quantities of beer. Because of later

13. Busch, Max: Ein Beitrag zur Frage der vollständigen Magenberstung, Frankfurt. Ztschr. f. Path. **30**:30, 1924.

14. Murdfield, P.: Akute Magenruptur nach Einnahme von Natrium Bicarbonicum, Klin. Wchnschr. **5**:1613, 1926.

distress, he took a "Messerspitze" of sodium bicarbonate. Severe pains soon appeared in the upper part of the abdomen, and at laparotomy the following day a tear, 5.3 cm. long, was found in the "Magenstrasse," 4.7 cm. from the cardia. The mucosa around the tear appeared normal, and there was no evidence of a perforating ulcer. The abdominal cavity contained from 6 to 8 liters of fluid and food. Murdfield believed that the huge quantities of beer and food led to overdistention and acute dilatation of the stomach; the addition of sodium bicarbonate caused the rapid formation of carbon dioxide, with the rupture occurring soon thereafter. In confirmation of this view, Murdfield stated that the introduction of 3 liters of from 0.3 to 0.4 per cent hydrochloric acid plus a "Messerspitze" of sodium bicarbonate into the stomachs of fresh cadavers led to the rapid formation of gas and frequently to rupture, always in the lesser curvature and nearer to the cardia than to the pylorus.

The third case, reported by Mariantschik,[15] was that of a man, aged 33, who ate salt herring and drank much water during the night. On the following morning, he drank a cup and a half of cocoa and went to work. Shortly afterward he jumped from his wagon, a distance of about two and one-half feet. One and one-half hours later he had sharp abdominal pains, which increased in severity. Laparotomy some hours later disclosed a perforation of the stomach near the pylorus. The wall around the site of rupture appeared normal, and no ulcer could be found.

SUMMARY

This paper presents the clinical history and observations at necropsy of a girl, aged 8, with chronic intermittent high intestinal obstruction, acute occlusion of the duodenum and rupture of the stomach. At about the level of the papilla of Vater, a membranous septum with a small iris-like aperture narrowed the lumen of the bowel. The dome of the bulging septum extended to the point at which the mesentery crossed the inferior horizontal portion of the duodenum. The marked hypertrophy of the wall of the duodenum oral to the septum, and that of the stomach, as well, indicated that the site of chronic obstruction was at this point. The acute occlusion was apparently caused by a plugging of the aperture in the septum by coarse food, aided by the mechanical hindrance offered by the crossing of the mesentery. The overadministration of enemas in an attempt to relieve the symptoms of an acute obstruction led, by overdistention and increased motor activity, to rupture of the stomach.

The reports of similar cases are reviewed.

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15. Mariantschik, L. P.: Ein Fall intraabdominaler Magenruptur traumatischen Ursprungs mit nachfolgender Perforation, Zentralbl. f. Chir. **53**:1050, 1926

REPEATED EXPOSURE TO HIGH TEMPERATURE

EFFECT ON LYMPHOID TISSUE AND ON LEUKOCYTE COUNT *

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It has been shown by Murphy and Sturm [1] that a single heating of mice for five minutes at a temperature of 60 C. is followed by a prompt fall in the total white cell count, both polymorphonuclear leukocytes and lymphocytes being affected. This initial fall was succeeded by a slow recovery of the polymorphonuclears and a rapid rise of lymphocytes which reached its peak at about the end of the second week and then gradually fell to the normal level. During the period of the most marked increase in the number of white cells, many lymphocytes were observed undergoing mitosis in the blood stream. Nakahara [2] studied the gross and microscopic pathologic changes in the group of mice mentioned and observed a marked enlargement of the lymph glands and spleen which reached its maximum on from the sixth to the eighth day, and by the fourteenth day had returned to normal. Immediately following the heating there were widespread degeneration and necrosis, followed in forty-eight hours by marked proliferation of cells of the germinal centers with many mitotic figures. On the fourteenth day, these organs again appeared to be normal. Nakahara concluded that the lymphocytosis thus induced was due, in part at least, to the enhanced proliferative activity of the germinal centers in the spleen and lymph glands which reacted to the destructive effect of heat on the lymphoid cells.

In view of the aforementioned observations, it seemed to be worth while to study the effects of repeatedly submitting mice to a high temperature on the lymphocytes of the blood, lymph glands and spleen. Each heating, after the first, was done at a time when the white cell count was at about its peak following the previous heating.

APPARATUS

The apparatus used consisted of a heating chamber made from a 10 inch (25.4 cm.) cylinder of asbestos, enclosing a 100 watt frosted electric light bulb in the lower portion of the cylinder and a small net wire cage above in which the

* Submitted for publication, May 21, 1929.

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1. Murphy, J. B., and Sturm, E.: J. Exper. Med. **29**:1, 1919.
2. Nakahara, W.: J. Exper. Med. **29**:17, 1919.

mice were placed. A thermometer was suspended between the top of the bulb and the cage. By the use of compressed air it was possible to maintain proper ventilation and a constant temperature, thus lowering the mortality rate during the heating. In the various groups heated in this manner a temperature of from 60 to 65 C. was maintained over a period of five minutes.

EXPERIMENTS

Group 2A.—Group 2*A* consisted of ten mice, the average normal white cell count of which was: 4,300 polymorphonuclear leukocytes and 7,600 lymphocytes. These mice were heated for five minutes at a temperature of 60 C. at ten day intervals, blood counts being made on only two or three mice before and after each heating, since it has been shown that too frequent counts on the same animal cause a wide fluctua-

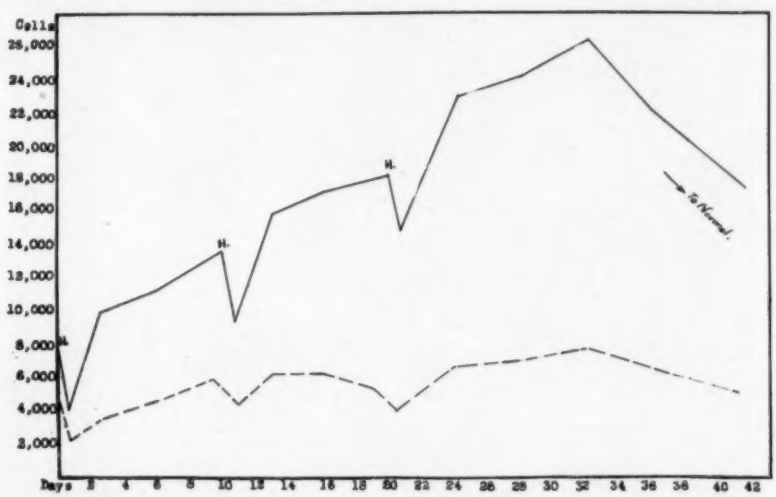

Fig. 1.—Composite leukocyte curve for group 2*A* (ten mice) heated three times. The solid line represents the lymphocytes; the broken line, the polymorphonuclear leukocytes, and *H*, the points of heating.

tion. Although this group was heated only three times, it is recorded principally to show the enormous rise in the number of lymphocytes that can be produced by repeated subjections to high temperature (fig. 1).

The initial fall in both polymorphonuclear leukocytes and lymphocytes immediately following exposure to heat was noted, with a slow rise of the former and a rapid rise of the latter. On the tenth day after the first heating and with the lymphocytes showing an increase of 6,000 cells above normal, the mice were heated a second time, again resulting in the initial fall followed by a rise in lymphocytes, but little or no change in the polymorphonuclear cells. On the twelfth day following

the third heating, the white cell count reached its peak. The count at this time was: 7,800 polymorphonuclear leukocytes and 26,600 lymphocytes, making a total white cell count of 34,400 cells per cubic millimeter. Subsequent counts showed a gradual fall to normal.

Groups 1B and 2B.—For the purpose of recording both tissue sections and blood picture, these two groups have been combined. The two groups consisted of seven mice each, the average normal white cell count being 3,900 polymorphonuclear leukocytes and 8,000 lymphocytes. The heating procedures were carried out in a manner similar to that described; these groups, however, received fourteen heatings and were observed over a period of 210 days (fig. 2).

During the first forty days, the observations on the blood picture of this group were essentially similar to those of the previous group

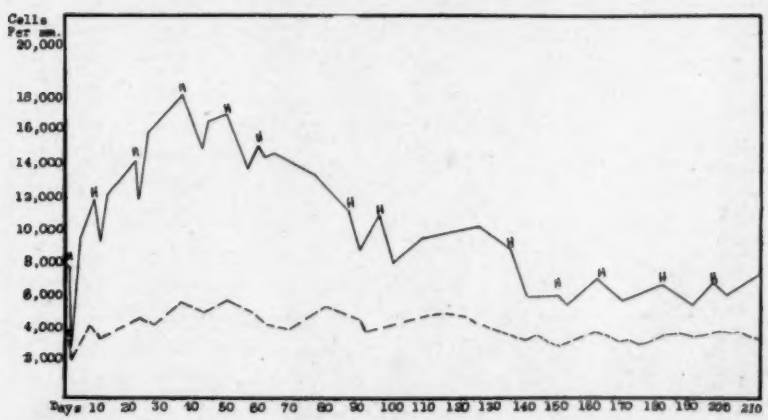

Fig. 2.—Composite leukocyte curve for groups 1 *B* and 2 *B* (fourteen mice) heated thirteen times. The solid line represents the lymphocytes; the broken line, the polymorphonuclear leukocytes, and *H*, the heatings.

recorded, there being always the initial fall in the number of both polymorphonuclear leukocytes and lymphocytes followed by a slow recovery of the former and a more rapid rise of the latter after each heating. During the initial period, there was a stairstep rise in the number of white cells, primarily lymphocytes, up to 25,000 cells per cubic millimeter. From this point, however, the number of white cells, principally lymphocytes, began to fall gradually, and little fluctation was noted following subsequent heatings. During the last thirty days of observation, the white cells were found to be at or below the normal count.

Sections of the spleen made immediately following the heating procedure, at a time at which the circulating white cells were at their lowest level, showed a marked necrosis, principally of the cells of the germinal

centers; sections made forty-eight hours later from a spleen that was grossly four times the normal size and at a time at which the circulating white cells were gradually rising, the germinal centers were much larger than normal and showed definite evidences of proliferation, the most important of which was the presence of many cells undergoing division. Our results, therefore, confirm those of Nakahara.[2]

Sections made ninety days after the initial heating showed a generalized increase in fibrous tissue in the spleen. The progressive increase in fibrous tissue was largely at the expense of the germinal centers and splenic corpuscles. After 210 days, when the circulating white cells

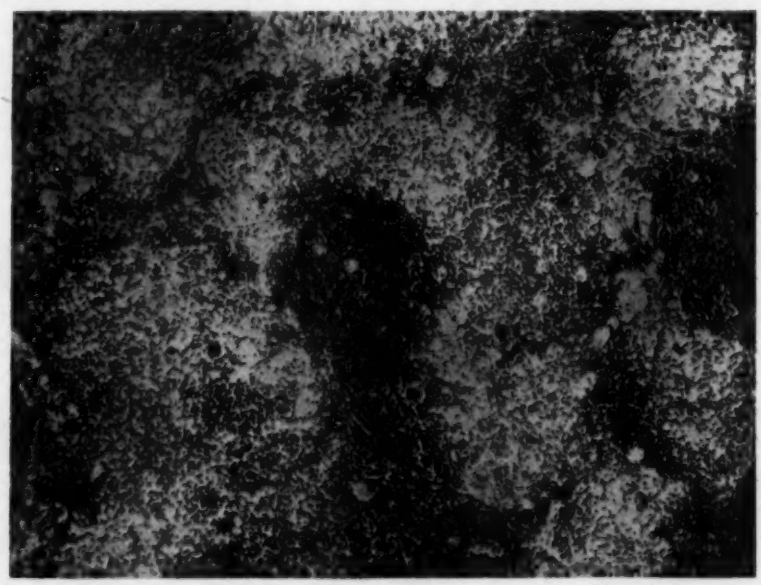

Fig. 3.—Fibrosis of the spleen after thirteen heatings or 210 days after the first heating; × 10.

were below the normal level, the spleen showed a marked diffuse fibrosis, patchy in distribution, with irregular areas of dense fibrous tissue that had replaced much of the normal splenic tissue. These areas made up 50 per cent or more of the spleen at this stage. Between these patches of fibrosis were areas of varying lymphoid content, irregular in outline, but generally of small dimensions (fig. 3).

Recently, we have subjected a small series of splenectomized mice to a similar heating procedure after complete recovery from the operation. In this group of animals the initial fall following heating was similar to that of the previous groups, but the rise in the number of lymphocytes was much slower and the maximum increase much smaller.

COMMENT

Repeatedly subjecting mice to dry heat at 60 C. at intervals of ten days results in the following changes in the leukocytes of the circulating blood:

(*a*) Soon after the heating there is a marked leukopenia followed by a marked rise in the number of white cells, which reaches the maximum number from ten to fourteen days later. The chief change in each instance was in the lymphocytes.

(*b*) In these experiments, this increase reached its peak about ten days after the third, and forty days after the initial, heating. At this time, in one series of animals the total white cell count reached a maximum of 34,400, of which 77 per cent were lymphocytes.

(*c*) After the fourth heating, each subjection to high temperature produced successively less and less effect and the number of white blood cells in the circulating blood gradually diminished. In one series of mice the total white cell count on the fortieth day was 23,700, of which 76 per cent were lymphocytes. In this same series, on the 200th day and after thirteen heatings the total number of white cells was approximately 10,000, of which 60 per cent were lymphocytes. The normal leukocyte counts of these mice was slightly more than 11,000, with an average of 65 per cent of lymphocytes. The lymphocyte counts of normal mice as reported in the literature have varied between a total of 5,000, with 62 per cent lymphocytes (Young [3]); 8,000 to 10,000 with 71 per cent lymphocytes (Goodall [4]), and 6,000 to 11,000 with from 50 to 60 per cent lymphocytes (Simonds [5]) per cubic millimeter. Murphy and Sturm [1] have recorded the highest allegedly normal leukocyte counts in mice of from 10,800 to 24,000, with from 54 to 65 per cent lymphocytes. The averages in our series, therefore, compare with the high normals of other observers, except those of Murphy and Sturm. The percentage of lymphocytes at the peak of the leukocytosis following heating of these mice exceeds considerably the maximum percentage recorded by any other observer. Hence, repeatedly heating mice at intervals of ten days results in a lymphocytosis which increases up to about the fortieth day, or the third or fourth heating, and then gradually subsides. The percentage of lymphocytes after 200 days, or twelve or thirteen heatings, is approximately normal. The maximum increase was 225 per cent above the original lymphocyte count for the series.

(*d*) During the period of heating the mice, the fluctuations in the number of polymorphonuclears were less marked than those in the

3. Young, J.: Edinburgh M. J. **28**:233, 1922.
4. Goodall: J. Path. & Bact. **14**:195, 1909.
5. Simonds: Anat. Rec. **30**:99, 1925.

number of lymphocytes. The peak was reached about ten days later than in the case of the lymphocytes. The maximum increase was about 70 per cent above the original normal.

The changes in the spleen and lymph glands following repeated heatings of the mice were:

(*a*) Localized areas of necrosis in the lymph glands and spleen in the first twenty-four hours, followed by a marked hyperplasia of the lymphoid elements, as pointed out by Nakahara. The alternating changes continue until about the fortieth day, or the third or fourth heating.

(*b*) After this time fibrosis begins and increases with each successive heating until after 200 days or from twelve to thirteen heatings, the spleen, although still much larger than normal, shows an extreme grade of fibrosis. At this time no lymph glands could be found on gross examination. On microscopic examination, sections of fat and connective tissue from the inguinal region failed to reveal lymphoid tissue.

The changes in the leukocyte count can apparently be correlated with the alterations in the spleen and lymph glands. Repeated heatings at intervals of ten days result in a marked lymphocytosis until fibrosis of the spleen and lymph glands begins. With increasing fibrosis, heating produces less and less effect on the blood picture until after about 200 days, or from twelve to thirteen heatings, the effect is negligible.

SUMMARY

Repeatedly heating mice at 60 C. for five minutes at intervals of ten days results in (*a*) a temporary lymphopenia, followed by (*b*) an increasing lymphocytosis up to about the fortieth day or the third or fourth heating. After this time each successive heating becomes less and less effective until, after about 200 days or twelve or thirteen heatings, the total leukocyte count and the percentage of lymphocytes return to or below normal and show little or no effect from further heating.

The diminishing effect of successive heatings on the leukocyte count after about the fortieth day is accompanied by an increasing fibrosis of the spleen and lymph glands.

IRON-INCRUSTED FIBER INCLUSIONS OF GIANT CELLS *

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Necrotic tissues and a variety of products resulting from degeneration of tissue act within the living host as foreign substances and stimulate the production of chronic granulation tissue, which commonly is designated a "foreign-body" tissue reaction.[1] Giant cells of the "foreign-body" variety are important constituents of these lesions, and they enclose or are closely approximated to the masses of the irritant substance. The certain identification by staining methods of some of the necrotic tissue substances or of their derivatives provoking the lesions is hindered at times or even thwarted because of the changes in their chemical composition or staining qualities accompanying degeneration, and because of incrustation with inorganic substances such as the salts of iron and calcium. Among the tissue substances commonly acting as foreign bodies are derivatives of the stroma, particularly elastic tissue fibers. Elastic fiber inclusions seem to have been observed in giant cells many years ago. Rona's [2] report of 1900 stated that Ssudakewitsch in 1889 first accurately described elastic fiber inclusions of giant cells, but before this, Virchow, Billroth, Schuppel and Lang had seen them. The giant cells with elastic fiber inclusions seen by Rona were in tuberculous and leprous lesions of the skin. He discovered that these fibers were incrusted with iron, and concluded that a degeneration of the elastic fibers within the giant cells favored the selective adsorption of iron diffused in the tissues. Hektoen,[3] in 1902, reported to the Chicago Pathological Society elastic fiber inclusions of giant cells in a healed hemorrhoid nodule and in tissues of an enlarged and bulbous nose. The fibers in the hemorrhoid nodule, only, contained iron.

Elastic fibers incrusted with calcium and iron causing inflammatory reactions have been observed a number of times in lung tissues.

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* Submitted for publication, May 20, 1929.
* From the Henry Baird Favill Laboratory, St. Luke's Hospital.
* Aided by the Winfield Peck Memorial Fund.

1. Haythorn, S. R.: Multinucleated Giant Cells, Arch. Path. **7**:651 (April) 1929.

2. Rona, P.: Ueber das Verhalten der elastischen Fasern in Riesenzellen, Beitr. z. path. Anat. u. z. allg. Path. **27**:349, 1900.

3. Hektoen, L.: The Absorption and Incrustation of Elastic Fibers in Giant Cells, Tr. Chicago Path. Soc. **5**:51, 1902.

Bittroff [4] saw them in the lungs of a woman 25 years of age who had a marked chronic passive hyperemia due to cardiac decompensation. Many giant cells with elastic fiber inclusions were seen in the histiologic preparations of the lungs. The inclusions reacted specifically with the microchemical tests for iron and calcium, and to some extent with the stains for elastic fibers. Bittroff concluded that the fibers were degenerated elastic tissue impregnated with iron and calcium. A similar report, he stated, had been made by Kockel. Schum,[5] in 1912, reported similar changes in the lungs of a man 47 years of age who for many years had had chronic asthma. He referred to other reports by Davidsohn and Krückmann. Gignon,[6] the next year, published another account of iron and calcium incrustations of tissue fibers in the lungs with chronic passive hyperemia. These tissue derivatives were found both intracellularly and extracellularly. Kraus [7] somewhat later reported the results of a comprehensive study of siderotic lesions of the spleen from a woman 47 years of age who had lymphatic leukemia. Some of the pigment deposits, he believed, were hemosiderin, some, hematoidin or a precursor, and others, greenish-yellow and arranged in coarse and fine bands, sometimes in wisps and sprays, he considered to be, at least in part, iron phosphate. He found the last-mentioned deposits chiefly in hyalinized fibrous tissue, but could not establish their absence in the connective tissue fibers themselves. Kraus previously had seen similar pigmentations in old infarcts of three spleens, and after the completion of his extensive study, saw them in another old infarct scar of the spleen and also in a markedly atrophic spleen. Aschoff, in 1905, reported the presence of iron crystals in a leukemic spleen, and, in a personal communication to Kraus, expressed the belief that they were identical with those which he (Kraus) had studied. Iron incrustations of connective tissue fibrils with hemochromatosis and focal hemorrhages were reported by Schuppisser.[8] In the spleen, he found the collagenous and the elastic fibers incrusted with iron, and he referred to a statement by Ehrlich that elastic fibers of living tissues in the vicinity of hemorrhages had the peculiar property of becoming impregnated with compounds of iron. Schuppisser believed that the compounds in his

4. Bittroff, R.: Ueber kalk und eisenhaltige elastische Fasern in der Lunge, Beitr. z. path. Anat. u. z. allg. Path. **49**:213, 1910.

5. Schum, H.: Bildung von Fremdkörper Riesenzellen um degenerierte elastische Fasern, Virchows Arch. f. path. Anat. **208**:446, 1912.

6. Gignon, A.: Eisen und Alkaliemprägnation des Lungengewebes, Beitr. z. path. Anat. u. z. allg. Path. **55**:46, 1913.

7. Kraus, E. J.: Ueber ein bisher unbekanntes eisenhaltiges Pigment in der menschlichen Milz, Beitr. z. path. Anat. u. z. allg. Path. **70**:234, 1922.

8. Schuppisser, H.: Ueber Eiseninkrustation der Bindegewebsubstanzen bei Hämochromatose und bei lokalen Blutungen, Virchows Arch. f. path. Anat. **239**: 320, 1922.

tissues were the hydroxide and phosphate of iron. Sigmund[9] also reported iron deposits in the spleen like those described by Kraus. He had seen them in old infarcts of the spleen and stated that they occur in the spleen with hemolytic icterus and so-called Banti's disease. The deposits are visible macroscopically as brown spots in the trabeculae of the spleen, usually associated with changes in the walls of the blood vessels. These iron deposits, he stated, are present especially in the elastic fibers which become necrotic and break up into segments, and are surrounded by foreign body giant cells. In unstained sections, the pigment is yellow-green or some similar color; usually it is associated with hemosiderin and hematoidin, and originates from the disintegrated blood of hemorrhages. Lubarsch,[10] commenting on the siderotic nodules of the spleen described by others, stated that these contain connective tissue fibers infiltrated with calcium or iron, or both, in the form of curious structures, in coils, granules or other shapes. The peculiarity of this pigmentation is that much is not in cells, but is an infiltration of the stroma fibers and vessel walls. Lubarsch saw these incrustations in an ovary and in an old infarct of the spleen in which both elastic and collagenous fibers were incrusted with iron and calcium. These fibers had stimulated a foreign body tissue reaction. Lubarsch referred to a similar observation by Talmann[11] in an aberrant nodule of splenic tissue. Other reports of iron and calcium incrustations of the spleen have been made by Christeller and Puskeppelies,[12] Klinge,[13] Nicod,[14] Pick[15] and Hennings,[16] and these authors refer to Eppinger's original observation. More recently Hogenauer[17] added another report. Pick stated that in addition to the vascular and perivascular destruction of the elastic and collagenous tissue elements in the spleen

9. Sigmund: Demonstration ungewöhnlicher Eisenablagerungen, Centralbl. f. allg. Path. u. path. Anat. **33**:207, 1922-1923.

10. Lubarsch, O.: Ueber die hämoglobinogenen Pigmentierungen, Klin. Wchnschr. **4**:2137, 1925. Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie **1-2**:480, 1927.

11. Talmann, I.: Nebenmilzen im Nebenhoden und Samenstrang, Virchows Arch. f. path. Anat. **259**:237, 1926.

12. Christeller, E., and Puskeppelies, M.: Die periarteriellen Eisen-und Kalkinkrustationen in der Milz, Virchows Arch. f. path. Anat. **250**:107, 1924.

13. Klinge, F.: Ueber die Entstehung der periarteriellen Eisen-und Kalkinkrustationen in der Milz, Virchows Arch. f. path. Anat. **255**:599, 1925.

14. Nicod, J.: Essai d'analyse d'un pigment ferrique rare, Schweiz. med. Wchnschr. **8**:200, 1924; abstr. Centralbl. f. allg. Path. u. path. Anat. **36**:81, 1925.

15. Pick, L.: Zur Frage der Eisen-und Kalkablagerung in der Milz, Klin. Wchnschr. **4**:517, 1925.

16. Hennings, K.: Ein Beitrag zur periarteriellen Kalk-Eiseninkrustation der Milz, Virchows Arch. f. path. Anat. **259**:244, 1926.

17. Hogenauer, F. Zur Frage der ausgedehnten Eiseninkrustation in der Milz, Virchows Arch. f. path. Anat. **269**:685, 1928.

and their incrustation with iron there is calcification of the incrusted structures, then a demarcation of the focus by chronic granulation tissue, a fibrous tissue encapsulation and the formation of foreign body giant cells in the granulation tissue. He gives as essential factors: (1) an increased destruction of the red blood cells following hemorrhage and leading to a maximal production of hemosiderin, and (2) a destruction of the elastic and collagenous tissues in sclerotic vessels or scars, which provide the matrix that becomes saturated with dissolved hemosiderin.

Such foreign-body reactions toward derivatives of stroma tissues, incrusted with iron compounds, have been observed at St. Luke's Hospital, Chicago, in tissues removed surgically from various places.

CASE 1.—Both fallopian tubes and the fundus of a uterus were removed surgically from a woman, aged 29, by Dr. A. H. Curtis. The tubes were 8 cm. long and from 1.7 to 2 cm. in diameter. The proximal end of each was rounded and sealed by fibrous tissue. Within the lumen of one was a small amount of red-brown fluid, and in the other, a thick yellow exudate. The linings were white and scarred in a number of places. In sections stained with hematoxylin and eosin, the lining of the fallopian tubes was thickened by masses of tuberculous chronic granulation tissue with focal round or oval structures histologically tubercles. In these were Langhans giant cells and also others, equally large, of the foreign-body variety. Within such giant cells or closely approximated to them were coarse fibril inclusions, several wrapped together like the layers of an onion. These, with a little granular substance, usually were in a clear portion of the cell. The staining qualities of the inclusions were as follows: with phosphotungstic acid-hematoxylin, yellow; Mallory's aniline blue, blue; van Gieson's connective tissue stain, lavender to red; Foot and Ménard[18] silver stain for reticulum fibers, dark red; Weigert's elastic tissue stain, faint lavender; Verhoeff's elastic fiber stain, variable-dark purple or green-yellow; ammonium sulphide test for iron, brown-black; potassium ferrocyanide test for iron, blue—a few red. In preparations stained for acid-fast bacilli, slightly curved, rodlike structures were found in the granulation tissue histologically tuberculous.

CASE 2.—The lymph node was contained in axillary fat removed with a mammary gland from a woman, aged 60, by Dr. S. M. Harsha because of carcinoma. The histologic preparations of the lymph node were without tumor, but they contained discrete and confluent masses of chronic tuberculous granulation tissue with the usual Langhans giant cells and also foreign-body giant cells with inclusions composed of coarse, concentrically arranged fibrils (fig. 1). The staining reactions were essentially the same as those mentioned in case 1. Granular, rodlike structures resembling tubercle bacilli were found in sections stained for acid-fast organisms.

CASE 3.—A cervical lymph node was removed for diagnosis by Dr. H. E. Jones from a negress, aged 24, with sickle cell anemia. The histologic preparations included large masses of chronic tuberculous granulation tissue with oval or round tubercles containing Langhans giant cells and foreign-body giant cells with inclusions of coarse concentrically arranged fibrils or hyaline masses like those men-

18. Foot, N. C., and Ménard, M. C.: A Rapid Method for the Silver Impregnation of Reticulum, Arch. Path. **4**:211 (Aug.) 1927.

tioned. The staining reactions, also, were in every respect as stated. Several structures resembling acid-fast bacilli were found.

CASE 4.—The tissues were removed by Dr. E. W. Ryerson from the dorsal surface of the foot of a white woman, aged 20. The incision made in correcting a simple bone deformity failed to heal. The surgical gauze dressings were regularly stained with bright red blood. For a long time the indolent nature of the ulcer was without explanation. Cultures of the exudate in the wound and of the tissues removed failed to demonstrate bacteria other than those usually present

Fig. 1.—Photomicrograph to illustrate the concentrically arranged, iron-incrusted fiber inclusions in two giant cells (case 2); × 515.

on skin surfaces or fungi which could be considered accountable for the chronic ulcer. Finally, the suspicion, entertained for some time, that this patient was malingering, was verified. In histologic preparations there was a chronic non-specific granulation and scar tissue reaction of the corium and subcutaneous tissues, and on the surface of the ulcer was an acute exudate. Some of the cellular portions of the chronic granulation tissue included coarse granular masses of yellow-brown pigmented material, some extracellular, some within large mononuclear cells and some within giant cells of the foreign-body variety. Also, there

were coarse, yellow, linear structures like the fibrils of connective tissue. Some of these, with branched ends like the fructifications of a mycelium, had both yellow and purple portions in the hematoxylin-eosin stained preparations. Besides these were similar yellow structures transversely segmented and not unlike the segmentations of coarse mycelial threads. The stains mentioned were used in examining these tissues. The yellow fibrils had none of the staining reactions of connective tissue. Certain fibrils, slightly yellow, stained faintly blue with Weigert's elastic stain, and some of these were in tangled masses of coarse threads. The yellow masses and fibrils reacted strongly with the microchemical tests for iron. In the scar tissue were disarranged coarse fibers stained like elastic tissue.

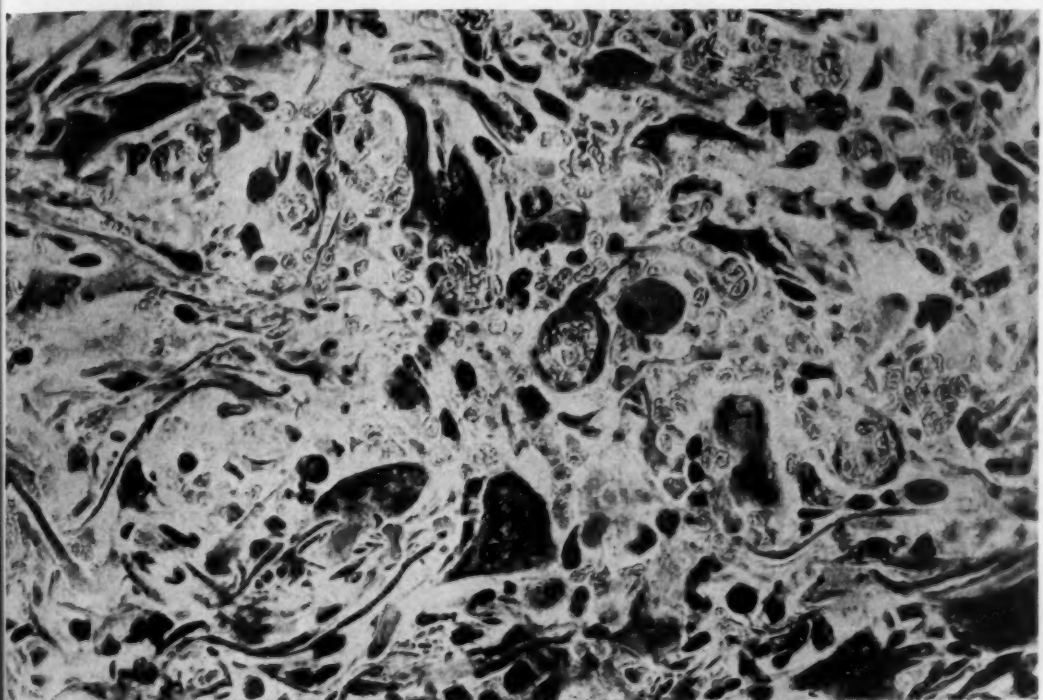

Fig. 2.—Photomicrograph of the granulation tissue with disarranged coarse fibrils and foreign-body giant cells (case 5). These fibers contained little or no iron; reduced from a magnification of × 515.

Case 5.—A mass of chronic granulation tissue was removed, by Dr. W. F. Lyon, from a draining wound of the forehead of a white man, aged 26, five months after a laceration of the soft tissues and a depressed fracture of the frontal bone, complicated by osteomyelitis. In this chronic granulation tissue were aggregations of foreign-body giant cells in close approximation to threads and coarse fibrils with a faintly yellow cast. These varied considerably in length and in their arrangement in the tissues (fig. 2). With the phosphotungstic acid-hematoxylin stain, many of these fibrils had the color of collagenous connective tissue, considerably diminished in intensity and with an affinity for the purple component of the stain. The microchemical reaction (prussian blue) for iron was negative or faint.

COMMENT

Connective tissue fibers with or without incrustations of iron and associated in the tissues of the host with foreign-body granulation tissue have been observed in tuberculous lesions of lymph nodes and fallopian tubes, and in nonspecific granulation tissue of the skin. The results with the stains for collagenous and elastic fibers are uncertain, and probably fibrils of both have initiated the foreign-body reactions and have become incrusted with the salts of iron.

ANAPHYLACTIC CROSSED RELATIONSHIP BETWEEN HORSE DANDER AND HORSE SERUM *

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It is generally assumed that there is some relationship between hypersensitiveness to horse dander and hypersensitiveness to horse serum. Positive skin reactions to both horse dander and horse serum, however, do not always appear in one person. The majority of these patients react to horse dander alone.

Longcope, O'Brien and Perlzweig,[1] in 1925, were the first to approach this problem from an experimental standpoint. They concluded that there was no crossed anaphylactic relationship between horse dander and horse serum. At about the same time, we were also engaged in studying this problem, and a preliminary report [2] was made in 1925, which appeared immediately after the publication of the experiments of Longcope and his co-workers. Contrary to their conclusions, we stated that a crossed anaphylactic relationship does exist. Our studies have been continued to the present time, and we are now prepared to present protocols in detail to substantiate our preliminary statement.

EXPERIMENTAL WORK

All the animals were normal.[3] Each animal was sensitized to either horse dander or horse serum and received a crossed injection of horse serum (or diphtheria antitoxin) or of horse dander extract. All animals not killed by the crossed shock injection were given a second shock injection one hour later of the

* Submitted for publication, May 27, 1929.

* From the Departments of Immunology and Pediatrics, University and Bellevue Hospital Medical College, New York University.

* This work is being carried on under "The Crane Research Fund for the Study of Allergic Diseases in Children."

* Read at the Joint Annual Meeting of the American Association of Pathologists and Bacteriologists and the American Association of Immunologists, Chicago, March 28, 1929.

1. Longcope, W. T.; O'Brien, D. P., and Perlzweig, W. A.: The Antigenic Properties of Extracts of Horse Dander: I. Active Sensitization of Guinea Pigs to Horse Dander Extract, J. Immunol. **10**:599, 1925.

2. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: The Anaphylactogenic Character of Horse Dander and Its Crossed Relationship to Horse Serum, Proc. Soc. Exper. Biol. & Med. **23**:16, 1925.

3. A number of years ago we learned the importance of being certain of the source from which animals are secured, especially when working with horse serum.

substance to which they were originally sensitized. In no instance was an animal used in which sensitization was not established.[4] Thus fifty-nine animals were eliminated from our protocols, for these animals would have invalidated any interpretation of a crossed reaction.

On the day of the experiment, the horse serum and dander[5] extract were run through a Berkefeld filter; the diphtheria antitoxin was that distributed by the New York City Department of Health for intravenous therapy.

Throughout our experiments the horse serum, dander extract and diphtheria antitoxin were controlled by the method of specific anaphylaxis. In all instances of death, necropsies were performed and deaths through anaphylaxis were acceptable only when the lungs remained fully ballooned after the wall of the chest was opened. All the intances regarded as definite anaphylaxis were of the severe type, demonstrating the following symptoms: marked dyspnea, convulsions, collapse, suffusion of the eyes, severe scratching and coughing. The instances of moderate anaphylaxis were those manifested merely by varying degrees of dyspnea.

Early in our work we learned that dander extract may have a primary toxic effect[6] if injected intravenously in amounts over 2 cc., and we therefore have in no instance given an animal an intravenous injection of more than 1 cc., the majority having received 0.5 cc. The same amounts of horse serum and diphtheria antitoxin were given.

Series I: Sensitizing Injection of Horse Serum—Crossed Shock Injection Dander Extract.—Group 1.—In this first group were guinea-pigs of different sizes that had received injections of horse serum at various times. The sensitizing injections varied from 0.2 to 10 cc. and were given either intraperitoneally or intravenously. After an incubation period of from several weeks to seven months, each animal received an intravenous injection of dander extract, ranging from 0.5 to 1 cc. The animals that survived this injection of dander were given from 0.5 to 1 cc. of horse serum intravenously about one hour later, in order to prove that they were originally sensitized to horse serum.

There were sixty-five animals in this group. Only two of these died in typical anaphylactic shock and five showed definite symptoms after the shock injection of dander extract; in other words, seven animals showed a crossed reaction when injections of horse serum were made as a sensitizing agent and horse dander extract as the shock agent.

Forty-seven animals that gave negative reactions after the injection of dander extract died in typical anaphylactic shock after the subsequent injection of horse serum. Eight of the eleven that remained showed marked anaphylaxis with recovery, and three showed only moderate symptoms.

To summarize, of sixty-five animals sensitized to horse serum, only seven showed crossed anaphylaxis after receiving injections of dander extract; fifty-eight did not demonstrate this crossed relationship. It is suggested by this group, therefore, that crossed anaphylaxis between horse serum and its homologous dander is difficult to demonstrate.

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4. Ratner, B., and Gruehl, H. L.: Investigations of Methods in the Study of Anaphylaxis, Proc. Soc. Exper. Biol. & Med. **26**:197, 1928.

5. Many different samples of horse dander were obtained from the Park Riding Academy at many different seasons of the year.

6. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Respiratory Anaphylaxis, Am. J. Dis. Child. **34**:23 (July) 1927.

GROUP 2.—There were eighteen animals in this group, weighing between 300 and 350 Gm. Each was sensitized by an intraperitoneal injection of 0.1 cc. of undiluted normal horse serum on Sept. 15, 1925. On October 2, seventeen days later, each received an intravenous injection of 1 cc. of dander extract. Two animals showed anaphylaxis with recovery; sixteen gave negative reactions. One hour later each received an intravenous injection of from 0.1 to 0.5 cc. of horse serum, and all died in typical anaphylactic shock.

Group 2, therefore, consists of a series of eighteen animals of practically uniform weight which were sensitized alike with small amounts of horse serum. Only two exhibited the crossed relationship to a moderate degree.

GROUP 3.—In this group there were thirteen animals, weighing between 350 and 500 Gm. Each received an intraperitoneal injection of 5 cc. of horse serum on June 8, 1928. On August 3, approximately two months later, each was given

TABLE 1.—*Crossed Anaphylaxis Between Horse Dander and Horse Serum* *

Number	Ip. Sens. Injection with DE, Cc.	Incubation Period	Result After Injection of 1 Cc. of HS, Iv.	Result After Injection of 1 Cc. of DE, Iv.
1	0.5	9 weeks	Death	—
2	1.5	9 weeks	Death	—
3	1.0	9 weeks	Death	—
4	1.0	9 weeks	Death	—
5	0.5	1 month	Death	—
6	0.5	9 weeks	Death	—
7	0.5	1 month	Death	—
8	0.2	16 days	Anaphylaxis with recovery	Positive uterine horn reaction
9	1.0	7 weeks	Anaphylaxis with recovery	Death
10	1.0	9 weeks	Anaphylaxis with recovery	Death
11	1.0	9 weeks	Anaphylaxis with recovery	Death
12	0.2	16 days	Moderate anaphylaxis	Death
13	1.0	6 weeks	Moderate anaphylaxis	Death
14	1.0	6 weeks	Moderate anaphylaxis	Death
15	0.2	16 days	Negative	Death
16	1.0	27 days	Negative	Death
17	0.5	9 weeks	Negative	Death
18	1.5	6 weeks	Negative	Death

* The weight of the animals when sensitized was from 250 to 300 Gm.; when given the shock injection, from 350 to 500 Gm. DE represents alkaline extract of horse dander; HS, normal horse serum; Iv., intravenously; Ip., intraperitoneally; Sens., sensitizing; death, typical anaphylactic death with the lungs completely ballooned. These experiments were carried out in the fall of 1925.

an intravenous injection of 1 cc. of dander extract. Seven of these animals gave negative reactions, three showed definite signs of anaphylaxis with recovery (dyspnea, convulsions, collapse) and three showed moderate signs of anaphylaxis with recovery (moderate dyspnea). One hour later, each received 0.5 cc. of horse serum intravenously, and all showed typical anaphylactic shock; nine died and four recovered.

In group 3, animals were sensitized with fifty times the sensitizing dose of the previous group. A higher degree of crossed sensitivity was manifested, six of thirteen animals showing moderate anaphylaxis.

Series II: Sensitizing Injection Dander Extract—Crossed Shock Injection Horse Serum.—In this group we reversed the order. The sensitizing injection was dander extract and the shock injection, horse serum. These results are given in table 1.

Of a total of eighteen animals, therefore, seven died in acute anaphylactic shock and seven showed symptoms of anaphylaxis with recovery after the crossed injection of horse serum.

Crossed anaphylaxis was exhibited with such regularity when horse dander was used as a sensitizing agent and horse serum as a crossed shock agent that we did not deem it necessary to carry out as large a number of experiments as in the former series.

Series III: Crossed Anaphylaxis with the Uterine Strip Method.—Fifteen guinea-pigs, weighing about 200 Gm., were sensitized by intraperitoneal injections of 1 cc. of either horse serum or horse dander extract. After an incubation period of from one to two months, the uterine horn was removed and was suspended in a 250 cc. bath of oxygenated Locke's solution at 37.5 C.; after it had assumed a normal base line, 1 cc. of the crossed antigenic solution was placed in the bath.

Five animals were sensitized with horse serum and crossed with dander extract. All gave negative reactions to the addition of dander extract, but a positive contraction when horse serum was placed in the bath. In this group there was no evidence of a crossed reaction.

The remaining ten animals were sensitized with dander extract. Three gave a positive contraction when horse serum was placed in the bath. All gave a positive contraction on the addition of dander extract.

In every experiment, the uterine horn was finally tested with a normal uterine contractor—0.001 Gm. of ergamine acid phosphate—to demonstrate that the muscle was still contractile and also to show its normal maximal contraction.

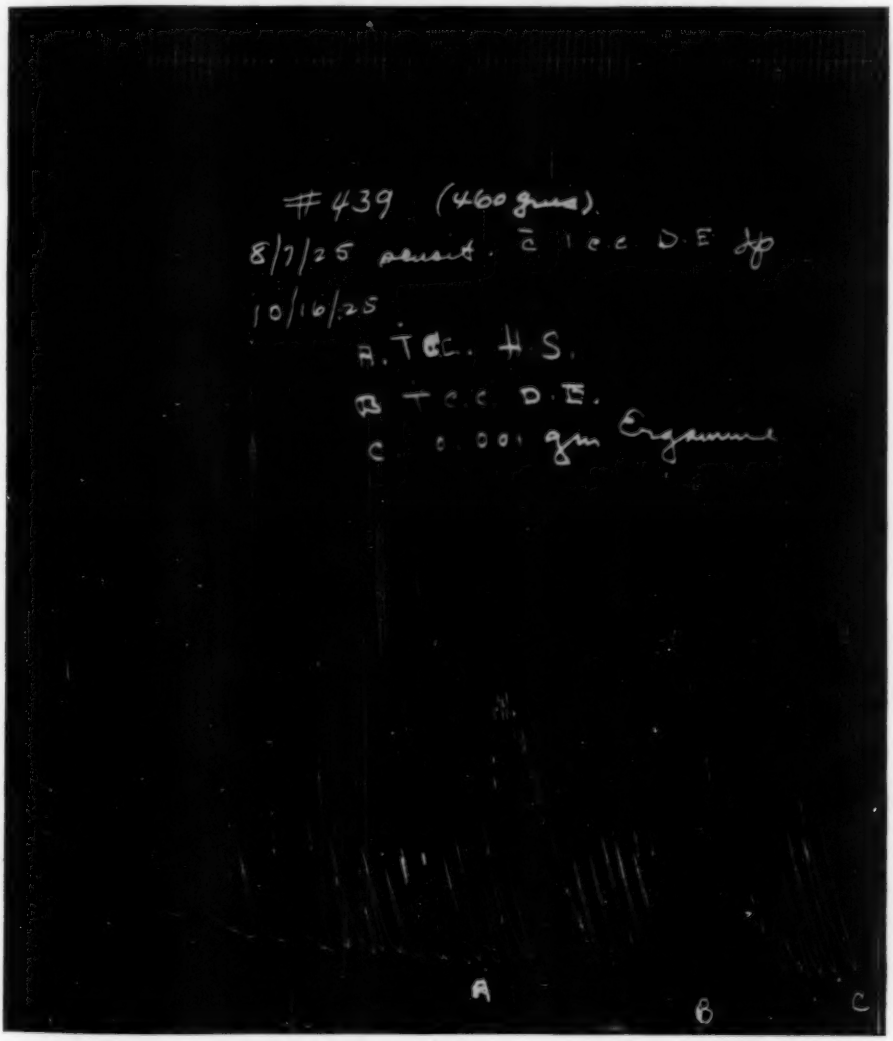
In the accompanying illustration the tracing shows the crossed reaction to horse serum of the uterine strip of an animal sensitized to horse dander. Several interesting points can be gathered from an analysis of this tracing. In the first place, it will be noted that when the crossed antigenic substance—horse serum—was placed in the bath, there was a definite contraction. After the base line was again established and the muscle had contracted normally for about sixteen minutes, dander extract was placed in the bath and an immediate uterine contraction was again manifested. This suggests that the first contraction to horse serum, owing to the common antigen present in horse serum and horse dander, did not bring about desensitization to the remaining antigenic elements in the horse dander. When the base line was reached after this contraction, ergamine was added to elicit a maximal contraction.

We did not continue further Dale experiments, for we believe that the Dale method is not as dependable as the intravenous route for determining a given state of hypersensitiveness.[4]

Series IV: Sensitization to Horse Dander—Crossed Shock Injection Diphtheria Antitoxin.—In order to show the position of antitoxin in this crossed relationship, the following experiments were carried out in the summer of 1928.

There were nineteen animals in this series, weighing between 300 and 400 Gm. Fourteen animals were sensitized with 0.5 cc. of dander extract intravenously and five with 5 cc. of dander extract intraperitoneally. The incubation periods varied

from nineteen days to four and one-half months. As a crossed shock injection, these animals received 0.5 cc. of diphtheria antitoxin intravenously. Two animals died in typical anaphylactic shock. These two were from the group previously noted with the large sensitizing injections and received injections after incubation periods of one and two months, respectively. Six animals manifested moderate



Virgin female guinea-pig sensitized by an intraperitoneal injection of 1 cc. of dander extract (DE); two months later, animal was killed by blow over the head and the Dale experiment performed. *A* represents the reaction to 1 cc. of horse serum; *B*, the reaction to 1 cc. of dander extract (DE), and *C*, the reaction to 0.001 Gm. of ergamine acid phosphate.

symptoms of anaphylaxis. The eleven remaining animals showed no crossed relationship after the injection of antitoxin. One hour after this injection all of the animals still alive were given an injection of dander extract intravenously; eleven died in acute anaphylactic shock and six showed definite anaphyiaxis with recovery.

Two of the nineteen animals died of shock and six showed moderate anaphylactic symptoms when sensitized with horse dander and given a shock dose of diphtheria antitoxin. The two that died had received the large sensitizing dose.

In order to demonstrate whether animals sensitized to horse dander dust by inhalation would give crossed anaphylactic reactions with horse serum, the following experiments were made.

Series V, Group 1: Nasal Sensitization with Dry Horse Dander—Shock Injection Horse Serum.—Thirteen animals were sensitized by the inhalation of dry horse dander. They were placed in the special "dust chamber" for a total of eleven hours from April 27 to May 4, 1926. On May 26, one month after the initial exposure, the animals were given intravenous injections of from 0.5 to 1 cc. of horse serum. Five showed only moderate symptoms of anaphylaxis after the crossed injection. One hour later, after an intravenous injection of 0.5 cc. of dander extract, four died in typical anaphylactic shock, and the fifth showed only moderate symptoms of anaphylaxis with recovery. Six of the remaining animals, all of which gave negative reactions after the injection of horse serum, died in typical anaphylactic shock and two manifested definite anaphylaxis with recovery after the injection of dander extract.

Group 2: Nasal Sensitization—Respiratory Anaphylaxis (Asthma) Followed by Crossed Injection of Horse Serum.—In this group there was a series of thirty animals, weighing approximately 350 Gm. each, which had been placed in the dust chamber for their initial sensitization to dry horse dander dust. They were exposed for from seven to eleven hours over a period of two weeks and were then permitted to live in a normal environment for from one to two months. After this incubation period, the animals were again placed in the dust chamber, and in all instances they demonstrated definite respiratory anaphylaxis (asthma). These animals were then each given an intravenous injection of 1 cc. of horse serum; one animal, No. 1013, showed marked dyspnea with moderate collapse and recovery, and seven animals showed only suggestive symptoms of crossed anaphylaxis. One hour later, each received injections of 0.5 cc. of dander extract. Animal 1013 showed the same marked symptoms; six of the seven that showed a suggestive crossed reaction died, and one manifested marked anaphylaxis with recovery after the injection of dander. Eleven of the twenty-two remaining animals died in typical anaphylactic shock, four showed marked symptoms, two showed moderate symptoms and five gave negative reactions.

In order to determine the influence of repeated attacks of respiratory anaphylaxis to horse dander dust on the degree of crossed hypersensitiveness, a series of eighteen animals was used. Of this series, only two showed moderate evidence of this crossed relationship. As the results are comparable to the original group, we do not feel it necessary to quote the protocols in full.

These animals, which exhibited definite respiratory anaphylaxis to horse dander dust, showed only a suggestion of crossed anaphylaxis to horse serum.

Series VI, Group 1: Nasal Sensitization—Crossed Injection of Diphtheria Antitoxin.—Twenty-two animals, weighing between 200 and 350 Gm., were exposed to dander for one hour daily in the dust chamber for from six to twelve hours. One month later, they were each given an intravenous injection of 0.5 cc. of diphtheria antitoxin.

In only two instances was there moderate dyspnea after the injection of antitoxin and both of these animals died after an injection of 0.2 cc. of dander extract. The remaining twenty animals gave negative reactions to the crossed injection, and after a subsequent injection of 0.2 cc. of dander extract ten died in acute anaphylactic shock, five showed marked anaphylaxis with recovery and five, moderate symptoms of anaphylaxis.

Group 2: Nasal Sensitization—Respiratory Anaphylaxis—Crossed Injection of Diphtheria Antitoxin.—Fifteen animals were sensitized by daily exposures of one hour each to dander dust for a total of eleven hours, beginning on Nov. 21, 1927. Five weeks later, when exposed in the dust chamber, they showed definite symptoms of respiratory anaphylaxis.

From three to eight weeks after their last contact with the dry dander they received an intravenous injection of 0.5 cc. of diphtheria antitoxin. Two animals showed a suggestion of crossed anaphylaxis and died after a subsequent injection of 0.5 cc. of dander extract.

One animal (420 Gm.) manifested severe respiratory anaphylaxis in the dust chamber and, four weeks later, after an intravenous injection of 0.5 cc. of diphtheria antitoxin died in typical anaphylactic shock with complete ballooning of the lungs.

The remaining twelve animals gave negative reactions after the crossed injection, but were proved to be highly sensitive to dander for all died in typical anaphylactic shock after an injection of dander extract.

Group 3: Nasal Sensitization—Repeated Attacks of Respiratory Anaphylaxis —Crossed Injection of Diphtheria Antitoxin.—In this final group there were twenty animals, weighing between 250 and 300 Gm. when initially sensitized and about 600 Gm. when receiving final injections. These animals were subjected to repeated contacts with horse dander in the dust chamber after they had been originally sensitized by inhalation. They manifested varying degrees of respiratory anaphylaxis at different times, and all received an intravenous injection of 0.5 cc. of diphtheria antitoxin from two to six months after their initial contact with dander.

Fifteen of this group gave negative reactions to the crossed injection. One animal, however, showed definite collapse with recovery, and four animals manifested moderate symptoms of anaphylaxis after the crossed injection. Four of these five animals died in typical anaphylactic shock and the fifth manifested definite anaphylaxis with recovery after the subsequent intravenous injection of dander extract. The fifteen animals that gave negative results after the crossed injection were proved highly sensitive by either death or severe anaphylactic symptoms after the injection of dander extract.

To sum up, of a total of fifty-seven animals sensitized to horse dander dust, nine showed varying degrees of crossed anaphylaxis and one died in anaphylactic shock after receiving injections of diphtheria antitoxin.

COMMENT

The foregoing protocols present a series of experiments in which we have studied the crossed anaphylactic relationship between horse dander and its homologous serum. The experiments are divided into six series.

In series I, there are three groups with a total of ninety-six animals. These animals received a sensitizing injection of undiluted normal horse serum, and after varying incubation periods received their second or shock injection of dander extract. There were only two deaths from this crossed injection of dander; ten animals showed definite crossed anaphylaxis and three, moderate anaphylaxis, making only fifteen positive crossed reactions from ninety-six animals.

It is interesting that the two animals that died had been given a rather large sensitizing dose. In the second group, in which we used a rather small sensitizing dose, there were fewer crossed reactions than in group 3 in which a larger sensitizing dose was used.

Series II, however, presents a strikingly different situation. When animals were sensitized to dander extract, it seemed to be much easier to produce a crossed reaction with horse serum. In this series there were eighteen animals, of which seven died in typical anaphylactic shock after the crossed injection, four showed definite anaphylaxis, three moderate symptoms and four gave negative reactions.

Series III graphically demonstrates by the Dale method the existence of this crossed relationship.

In series IV, the crossed relationship between dander sensitization and diphtheria antitoxin was studied. Here, too, is evidence that crossed reactions can be elicited, for two animals died of acute anaphylactic shock and six showed moderate symptoms after the crossed injection of diphtheria antitoxin. The two animals that died had received a large sensitizing dose.

In series V there are three groups, totaling sixty-one animals which were sensitized through the inhalation of dry horse dander. Of this series, only two showed a definite crossed reaction with horse serum, five showed moderate symptoms and eight gave suggestive reactions.

In the final series, we studied the crossed relationship between horse dander inhaled as an antigen and diphtheria antitoxin injected as a shock agent. Fifty-seven animals were sensitized nasally, and of these one died in typical anaphylactic shock after an injection of antitoxin. One animal showed marked anaphylaxis with recovery, six manifested moderate symptoms and two were only suggestive.

Table 2 summarizes the results of our experiments.

The statement of Longcope and his co-workers [1] that horse dander is specifically antigenic and bears no crossed relationship to horse serum is untenable. Our statement, appearing almost simultaneously in pre-

liminary form, that there is a crossed relationship appears to be correct, for Forster,[7] who has recently repeated these experiments, has found such a crossed relationship definitely to be present.

The outstanding peculiarity that we found early in our work was the fact that sensitization to horse serum and crossed shock reaction to horse dander was rarely consummated, whereas when animals were sensitized to horse dander, a much greater number gave a crossed reaction after an injection of horse serum. It is gratifying to note that Forster, with crossed precipitation reactions, found a much higher titer of crossing when antidander serum was used with horse serum as antigen than when antiserum against horse serum was titrated against horse dander. Forster's experiments with anaphylaxis in the animal bring out this peculiarity, for of twelve animals sensitized to horse dander, ten were fatally shocked by a crossed injection of horse serum, whereas of fifteen animals sensitized to horse serum, only three gave suggestive crossed

TABLE 2.—*Crossed Anaphylactic Relationship Between Horse Dander and Horse Serum*

Sensitizing Substance	Shock Substance	Total Number of Animals	Positive	Negative
Horse serum	Dander extract	96	15	81
Dander extract	Horse serum	18	14	4
Dander extract	Antitoxin *	19	8	11
Dander dust †	Horse serum	61	15	46
Dander dust	Antitoxin	57	10	47

* Antitoxin: New York City Department of Health diphtheria antitoxin.
† Dander dust: guinea-pigs sensitized by inhaling dry dander dust in "dust chamber."

reactions with horse dander. This relationship seems to be fairly definite.

We maintained that the final criterion for anaphylactic experimentation cannot rest with the uterine strip method. Our protocols show that fourteen of eighteen animals sensitized to horse dander manifested a crossed reaction to the injection of horse serum, whereas with the Dale method there were only three positive crossed reactions in ten animals sensitized to horse dander. It is curious to note that Forster obtained only two positive crossed reactions with the Dale method out of seven tests and showed ten positive crossed experiments with twelve animals receiving injections. These results are practically identical with ours. Since Longcope based his conclusions on only a few Dale experiments, this probably accounts for his failure.

The common factor resident in horse dander and horse serum is presumably present in very small amounts and is related to the globulins, for we had animals sensitized to horse dander that could be killed by an

7. Forster, G. F.: Is There an Immunological Relationship Between Horse Serum and Horse Dander? J. Exper. Med. **47**:903, 1928.

injection of diphtheria antitoxin. This antitoxin contains only pseudoglobulins.[8]

It has been noted by one of us (B. R.) that persons naturally sensitive to horse dander are, in the minority of cases, sensitive to horse serum in varying degrees. Some of these, however, are exquisitely sensitive to horse serum, though they have never received a previous injection of horse serum. A direct corollary may be drawn between such persons and the gunea-pigs nasally sensitized to horse dander and shocked by horse serum antitoxin.

CONCLUSIONS

From our experiments we conclude that horse dander and horse serum are antigenically related, the common substance being present in small amounts and related to the globulin fraction. This common substance is apparently present in smaller amounts in the horse dander than in the horse serum, since it is easier to sensitize an animal to horse dander and cause shock with horse serum than the reverse. Densitization does not occur after recovery from a crossed shock injection.

Nasal sensitization and respiratory anaphylaxis (asthma), induced in animals through the inhalation of dry horse dander, can result in horse serum hypersensitiveness, and such animals may be killed by an injection of horse serum antitoxic globulin.

It is suggested that this mechanism of natural sensitization to horse serum through the inhalation of horse dander is related to the problem of the hypersensitiveness of man to horse serum.

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8. Personal communication from Dr. Edwin J. Banzhaf, Research Laboratories, New York City Department of Health. The diphtheria antitoxin used in these experiments had had the albumin, euglobulin and fibrin removed and contained only the pseudoglobulins in a concentration of three times that found in normal horse serum. This antitoxin is heated to 58 C. for two hours. The antitoxin is distributed for intravenous administration.

THE RETICULO-ENDOTHELIAL SYSTEM OF THE RABBIT*

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The reticulo-endothelial system of the rabbit has been investigated by the introduction into the peripheral circulation of rabbits' red blood corpuscles stained with iron hematoxylin. Charles Bolton[1] used corpuscles stained with Ehrlich's acid hematoxylin in his study of absorption from the peritoneal cavity. The advantages of the use of corpuscles in the present study were that the injected particles were of uniform size, were normal inhabitants of the blood vessels and were easily identified in their ultimate situations. When care was taken in the preparation of the black erythrocytes, a suspension of them was obtained in normal solution without clumping.

EXPERIMENTAL WORK

Blood was aspirated from the rabbit's heart. It was defibrinated by whipping, and centrifugated. The serum was then pipetted off, and alternately washed with saline solution and centrifugated. Mordanting was performed with 2 per cent ferric alum for thirty minutes, and the preparation was allowed to stand overnight. It was then alternately washed with saline solution and centrifugated. For staining, 0.5 per cent aqueous hematoxylin was applied for thirty minutes or more. This was followed by alternate washing with sterile saline solution, and centrifugation. The corpuscles were fixed in 1 per cent formaldehyde for one hour. They were then washed with sterile saline solution and centrifugated. Sterile saline solution was added in the required amount.

During the mordanting and staining, it was found advisable to work with thin suspensions of cells in order to prevent clumping. The cells of the suspension could be counted in the same way as the cells of blood are counted, by a hemacytometer.

The saline suspensions of black erythrocytes were injected into the marginal veins of the ears of both normal and splenectomized rabbits. The animals were killed at periods varying from two hours to one week after the injection.

The number of cells injected varied from 1,000,000 to 121,000,000. The average rabbit erythrocyte count is about 7,000,000 per cubic millimeter. The ultimate destination of the black cells was the same whether a smaller or a larger number of cells was injected. The animal that received the largest number of cells died of pneumonia two days later, while another animal receiving 46,000,000, which was killed a

* Submitted for publication, May 21, 1929.

* From the Department of Pathology, Moukden Medical College, Manchuria.

1. Bolton, Charles: J. Path & Bact. **24**:429, 1921.

week later, presented by no means such numerous black cells as did the rabbits killed soon after the injection.

The length of time the black cells remained in the peripheral circulation was variable. Sometimes they disappeared quickly. In the case of the animal that had received 121,000,000 cells, there were still 4,687 per cubic centimeter twenty-four hours later. No "blood crises," such as Elvidge [2] recorded as following the intravenous injection of particles of quartz, india ink, carmine or trypan blue, were observed. In the animal that was allowed to live for a week after the injection, a noticeable increase of large mononuclear cells was present in the blood throughout this period, commencing during the second twenty-four hours.

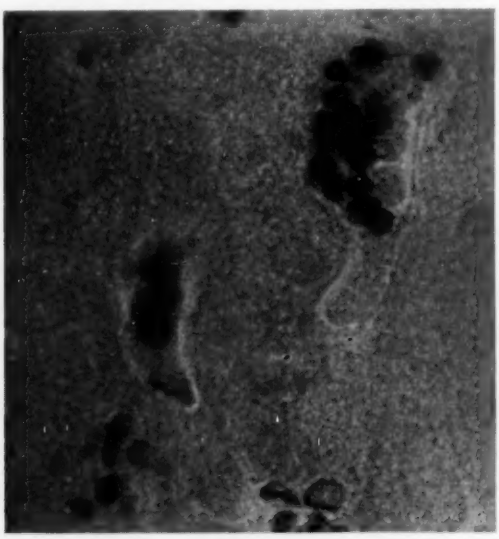

Fig. 1.—Kupffer cells of liver containing black erythrocytes.

POSTMORTEM EXAMINATION

The liver and the spleen were invariably black. The lungs were also dark. No other organs showed any change of color. In the splenectomized animals, the liver and the lungs were the only organs to show changes of color.

In the normal animals, the liver, the spleen and the lungs took up most of the black cells. The Kupffer cells of the liver often contained large numbers of them (fig. 1). In the spleen, the cells were also taken up in large numbers by the reticulo-endothelial cells of the pulp. When the pieces of the spleen were embedded in paraffin, after dissocia-

2. Elvidge, A. R.: J. Path. & Bact. **29**:325, 1926.

tion in weak chromic acid, the cells lining the splenic sinuses appeared free of the black erythrocytes. They were absent, also, from the central part of the malpighian corpuscles.

It was difficult to determine in the lungs (fig. 2) what cells were responsible for the phagocytosis. In the alveoli there seemed to be three possible sources, the cells lining the alveoli, the endothelium of the capillary in the alveolar wall or histiocytes lying deep to the alveolar lining. Aschoff [3] said that ordinary endothelium did not have any place in the reticulo-endothelial system, and Maximow [4] said that the endothelium was not able to produce histiocytes. Lang,[5] quoted by Bloom,[6] studied

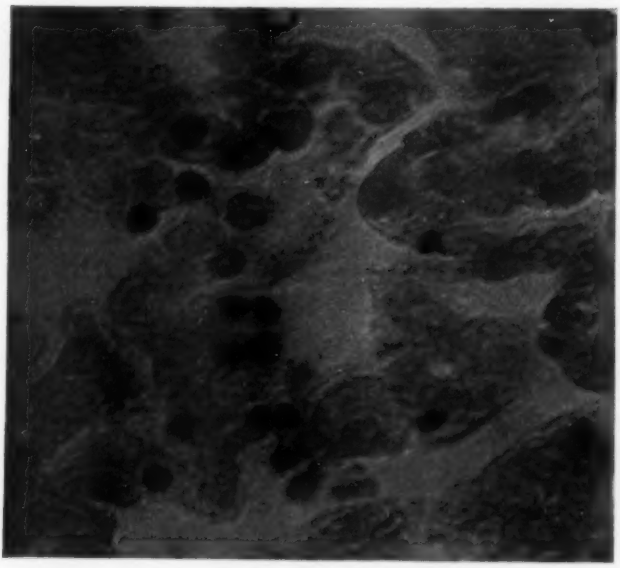

Fig. 2.—Black erythrocytes phagocytosed by alveolar cells of lung (histiocytes?).

cultures from the lungs of rabbits in great detail. He traced the alveolar phagocyte to the septum cells. The latter, he believed, are partially differentiated mesenchymal elements within and on the alveolar wall, which under such stimuli as bacteria or dust particles or

3. Aschoff, L.: Lectures on Pathology, New York, 1924, p. 16.

4. Maximow, A. A.: Morphology of Mesenchymal Reactions, Arch. Path. **4**:578 (Oct.) 1927.

5. Lang, F. J.: Arch. f. exper. Zellforsch. **2**:93, 1926.

6. Bloom, William: Immune Reactions in Tissue Culture: Reaction of Lungs from Normal and Immunized Rabbits to Pigeon Erythrocytes, Arch. Path. **3**:613 (April) 1927.

explantation develop into alveolar phagocytes. Fried [7] concluded from an experimental study of the origin of histiocytes in the lungs by the use of intratracheal injections of vital stain, that (1) the phagocytes in the pulmonary alveoli in inflammatory and congestive processes are macrophages or histiocytes and therefore cells of mesenchymal origin; (2) that these cells originate from the nucleated cells commonly spoken of as the (respiratory) epithelial cells lining the wall of the pulmonary alveoli, and (3) that the so-called epithelial cells lining the pulmonary alveoli are to all appearances not epithelial, but of mesenchymal origin —that is to say, they are histiocytes and belong to the reticulo-endothelial system.

The fact that the lungs took such an important part in the phagocytosis of the injected black erythrocytes, only less important than the parts played by the liver and the spleen, and exceeding in importance the parts played by the bone-marrow and the lymphatic tissue, as will appear later, seems to lead to the conclusion that the lungs form an important part of the reticulo-endothelial system in the rabbit.

The bone-marrow was somewhat variable in its content of black erythrocytes, sometimes presenting a scanty number and sometimes many. They were never so numerous as in the liver, the spleen and the lungs.

The lymphatic glands, whether mesenteric or in other situations, and the appendix, a large lymphoid organ in the rabbit, took up practically no black cells. Occasionally, one or two cells were seen in a section, but often none at all.

The kidneys showed sometimes a considerable number of black erythrocytes, either situated in intertubular cells or in the glomeruli. Other organs occasionally examined were the suprarenal glands and the pancreas. These each contained a few of the cells.

It was only in the liver and the spleen that the cells were present in masses. Elsewhere the cells were phagocytosed singly or in small groups of two or three or four. This was true even of the lungs, although their total content of black cells was great. This seems to indicate either a difference in the avidity with which the cells in the various parts of the reticulo-endothelial system phagocytose the black erythrocytes or a difference in the size of these cells.

The distribution of the phagocytosed erythrocytes in the splenectomized animals was precisely the same as in the normal animals. The liver seemed capable of entirely compensating for the absence of the

7. Fried, B. M.: Origin of the Histiocytes (Macrophages) in Lungs: Experimental Study by Use of Intratracheal Injection of Vital Stain, Arch. Path. **3**:767 (May) 1927.

spleen. Jaffé [8] stated that in several animals, such as the rabbit, mouse (M. B. Schmidt) and *Macacus rhesus* (Krumbhaar and Musser), the removal of the spleen caused a proliferation of the stellate cells of the liver. If this is the case, the compensation is easily accounted for, particularly as the spleen in the rabbit is a comparatively small organ.

The question arises whether the black erythrocytes are to be regarded merely as foreign bodies or as dead hemoglobin-containing blood cells. To determine this point, india ink was injected into the circulation of another rabbit, and its ultimate distribution compared with that of the black erythrocytes. It was found to be almost the same.

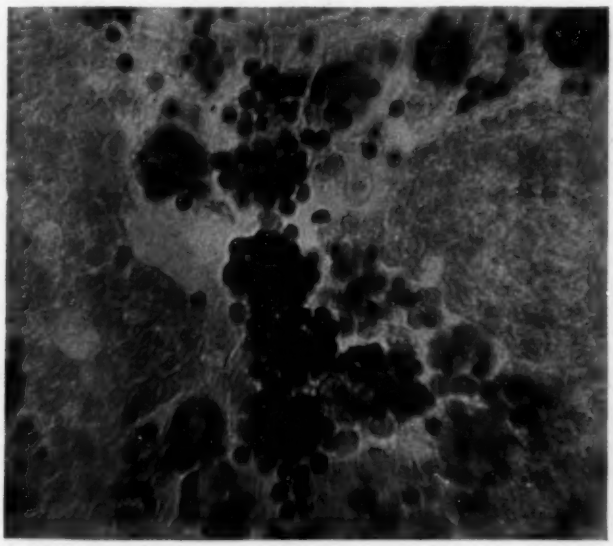

Fig. 3.—Cervical lymph gland, with multiple erythrocytes contained within the reticulo-endothelial cells of the lymph sinus.

The bone-marrow, however, was dark, unlike that of the animals which had received the injection of black erythrocytes. Microscopically, too, the carbon pigment was present here in great quantity in the reticulo-endothelial cells, although, for the most part, in small particles and in moderate amount in any one cell. Again, the lymphatic glands and the appendix were practically free of carbon particles, while the kidneys and the suprarenal glands contained them.

The mesenteric lymph glands of the rabbit are, to a considerable extent, hemolymph glands. They commonly contained many cells the protoplasm of which was full of phagocytosed red corpuscles. Vessels

8. Jaffé, R. H.: Reticulo-Endothelial System; Its Rôle in Pathologic Conditions in Man, Arch. Path. **4**:48 and 54 (July) 1927.

supported by a lymphoid sheath were not infrequent, reminding one of the lymphoid-sheathed arterioles of the spleen. Blood pigment was sometimes seen in these glands. These facts seem to point to a function analogous to that of the spleen. Even the cervical lymph glands of the rabbit helped on occasion in the destruction of the effete blood corpuscles (fig. 3). In a splenectomized rabbit, large numbers of fragmented polymorphonuclear cells were observed in the reticulo-endothelial cells of a cervical lymph gland. In this animal, these cells were also phagocytosed by the megakaryocytes of the marrow (fig. 4), so that these cells have other functions, in the rabbit, at any rate, than the formation of thrombocytes.

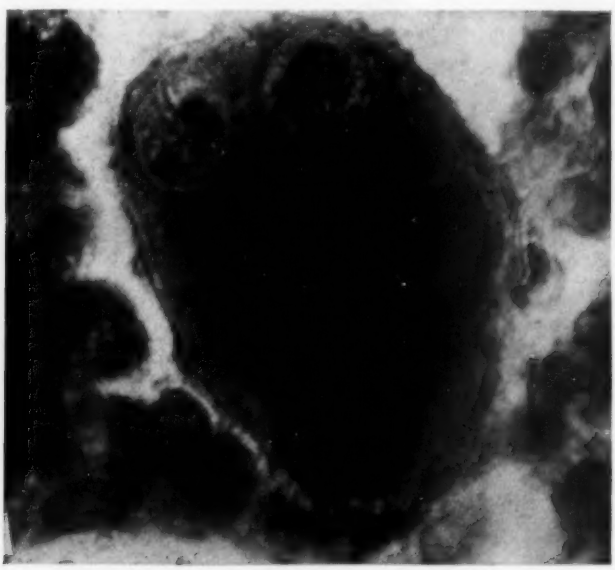

Fig. 4.—Megakaryocyte of bone-marrow containing three phagocytosed, partially digested polymorphonuclear cells.

The lymphatic glands of the rabbit, then, though playing an important part in the metabolism of blood pigment, did not seem to take any noticeable share in the phagocytosis of dead blood cells or of carbon particles injected into the peripheral circulation.

As has already been mentioned, the appendix, which in the rabbit is a large lymphoid organ, and the wall of which in the normal animal contains much pigment, also seemed to take no part in the phagocytosis of foreign particles injected into the peripheral circulation.

There seems to be, then, a differentiation of function in the various parts of the reticulo-endothelial system of the rabbit, and, where function is the same, a difference in ability to perform the function. Reference has already been made to the difference in numbers of

black erythrocytes taken up by the cells of the liver and the spleen, on the one hand, and by the cells of the lungs and other parts of the reticulo-endothelial system, on the other. There seems to be, also, a difference between the reticulo-endothelial cells lining the splenic sinuses and those of the pulp. It has already been stated that the cells lining the splenic sinuses did not take up the black erythrocytes. When india ink was injected into the circulation of the rabbit, although the spleen as a whole took up the carbon pigment in great quantity, this pigment was present in the sinus reticulo-endothelial cells in fine particles and in small amount, whereas in the cells of the pulp, the pigment was present in masses. It was difficult to make out this difference in the rabbit's spleen in sections prepared in the ordinary way, but when dissociation in weak chromic acid was carried out before the tissues were embedded, this could be clearly determined.

This difference in function in the various parts of the reticulo-endothelial system has been noticed in pathologic conditions in which blood is being destroyed. Jaffé [8] pointed out that while in infectious diseases the whole reticulo-endothelial system is usually involved in the process of destruction of erythrocytes, in the hemolytic anemias only certain organs show a predilection for the phagocytosis of erythrocytes. In pernicious anemia, as well as in hemolytic jaundice, the phagocytosis of red cells in the spleen is much less pronounced than it is in the other parts of the reticulo-endothelial system.

SUMMARY

A method of preparing rabbit's erythrocytes for injection into the circulation of other rabbits is described. The method makes them easily identifiable afterward.

Using this method, one finds that, in normal animals, the spleen, the liver and the lungs take up the major portion of the injected cells; the bone-marrow takes them up to a less degree, and other organs, such as the kidneys, suprarenal glands, etc., slightly; the lymphatic glands and the appendix take them up hardly at all. In splenectomized animals the distribution is the same.

The injected cells are phagocytosed in large numbers by the Kupffer cells of the liver, and by the cells of the splenic pulp, while they are taken up singly or in small groups by the reticulo-endothelial cells of the lungs, the bone-marrow and the other parts of the reticulo-endothelial system.

The importance of the lungs in the reticulo-endothelial system of the rabbit is pointed out.

Evidence is given showing that the lymphatic glands of the rabbit play an important part in the metabolism of blood pigment.

This distribution of the phagocytosed black erythrocytes and carbon pigment in the spleen, after injection into the peripheral circulation, is shown to differ in the cells lining the sinuses and in the reticulo-endothelial cells of the pulp.

On these grounds, two suggestions are made: that the various parts of the recticulo-endothelial system of the rabbit vary in function, and that the parts in which the functions are the same, are not equipotent.

THE DEVELOPMENT OF A CARCINOMA OF THE BREAST

REPORT OF A CASE * *

HELEN INGLEBY, M.B., M.R.C.P.

PHILADELPHIA

History.—A single woman, aged 42, was admitted to Woman's College Hospital in the service of Dr. Margaret Sturgis. She complained of a tumor of the right breast of two months' duration. It was situated in the inner and upper quadrant, and when first noticed was the size of a peanut. The menses were regular. The last menstrual period had begun on Nov. 27, 1928. The operation took place on Dec. 21, 1928, i. e., four days before the next period was due. The past history of the patient was unimportant. Her mother had died of carcinoma of the breast at the age of 39.

On admission, a hard tumor the size of an egg was found in the upper inner quadrant of the right breast.

The tumor was excised locally and reported on at once. Halstead's operation for removal of the breast was then carried out.

Macroscopic Examination.—The main growth measured about 2 by 3 cm., and was densely adherent to the surrounding breast tissue. It felt hard and cut "like an unripe pear." The breast itself was rather nodular. A small, hard nodule, the size of a millet seed, was found near the muscle, and proved to be a secondary growth. Paraffin sections were made from the main tumor and from various parts of the breast and stained with hematoxylin and eosin. Three of four sections of breast showed growth, and metastases were present in the glands.

Microscopic Examination.—The main tumor consisted of atypical, more or less polygonal cells with irregular nuclei, most of which stained moderately deeply. Mitotic figures were numerous. There was little fibrous tissue but enormous numbers of small round cells, mainly lymphocytes. The malignant cells appeared to have developed in ducts, and remains of distended ducts could be seen around most of the clumps. The tumor shaded off into normal breast tissue showing the typical premenstrual phase of proliferation. This part of the section was particularly interesting because in it the transition of physiologic proliferation into carcinoma could be clearly followed.

In the unaffected lobules, the ductules showed the following normal characters (fig. 3): They were lined by relatively small, more or less cuboidal cells, in each of which the nucleus occupied the greater part of the cell. The nuclei were somewhat irregular in size and shape. Most of them were oval, the long axis of the nucleus being at right angles to the duct. For the most part, they stained deeply owing to the dense, fine, chromatin meshwork that they contained. In the resting state, the nuclei were small and stained deeply. As the premenstrual phase was approached, they enlarged, the chromatin meshwork was spread apart and therefore the whole nucleus appeared lighter. For this reason, the largest

* Submitted for publication, May 31, 1929.

* From the Department of Pathology of the Woman's Medical College of Pennsylvania.

nuclei in our sections of normal ductules tended to appear pale. They also lost their characteristic shape and became round. The nuclear membrane was always well defined, and there was usually a fairly definite nucleolus. The protoplasm was scanty, except when premenstrual secretion was actually going on, and then the cell was seen to be columnar, the protoplasm being collected toward the lumen. The cell outlines were not clear. The nuclei were basal and close together, often nearly touching each other. Sometimes their arrangement was a little irregular, and in the larger ductules more than one layer of cells was usually visible. The

Fig. 1.—A photomicrograph of tumor of the breast, showing (*a*) a distended duct filled with carcinoma cells, and (*c*) a lobule in the premenstrual stage of development.

cells of the basement membrane participated in the premenstrual growth, the nuclei being ovoid and plump and the protoplasm sometimes a little vacuolated. Around each duct was a narrow band of hyaline connective tissue. This became broader and more conspicuous the nearer the ductules were to the tumor. Spaces between them were filled with loose, rather edematous, fibrillary meshwork. In some areas, the ductules showed a wider lumen than in others, and some contained secretion.

The first sign of a malignant change was an increase in the size of the cells lining the ductules. Figure 4 shows the earliest changes that could be detected. The chief abnormality was that the nuclei of some cells, although not larger than those often found in the premenstrual breast, were larger than any seen in the normal ductules of this particular specimen. They were unduly pale and a little irregular in outline. This alone would not class them as carcinomatous. I have seen similar cells in other breasts in the late premenstrual phase. More significant, taken in conjunction with these observations, was the broad band of hyalin

Fig. 2.—A photomicrograph of tumor of the breast showing a distended duct (*a*) filled with carcinoma cells down to its terminal branches (*b*), which are ending in the lobule (*c*). Some ductules in *c* are carcinomatous, others are not. *a'* indicates a similar carcinomatous duct; *c'* and *c''*, other partly carcinomatous lobules.

that surrounded the ductule. The periductal fibrous tissue degenerated in the breast pari passu with proliferation of the epithelium, and the broad band of hyalin probably represented excessive degeneration and compression of this surrounding connective tissue.

In figure 5, a ductule is shown in which the lesion had progressed a step further. All the cells were hypertrophied, and the two largest would have been

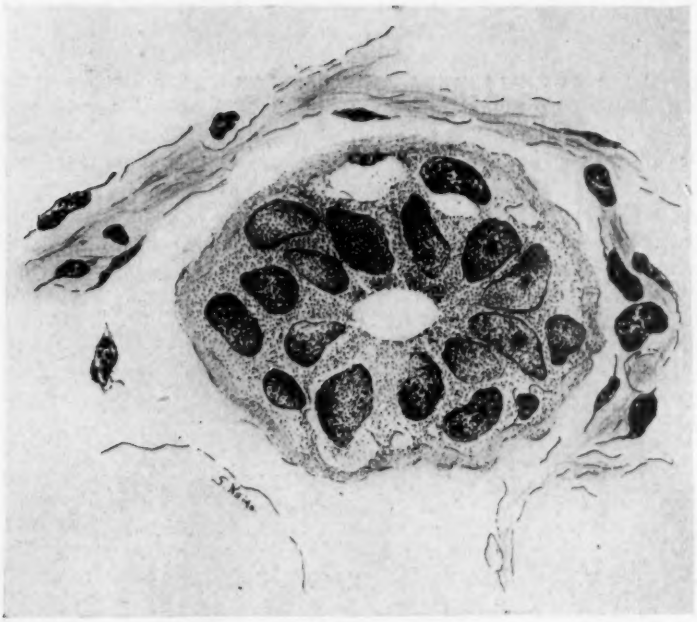

Fig. 3.—A normal premenstrual ductule from a noncancerous part of the breast operated on for tumor.

Drawings 3 to 6 were made with camera lucida under 1/12″ Zeiss oil immersion; no. 4 eyepiece; tube length, 140 mm.

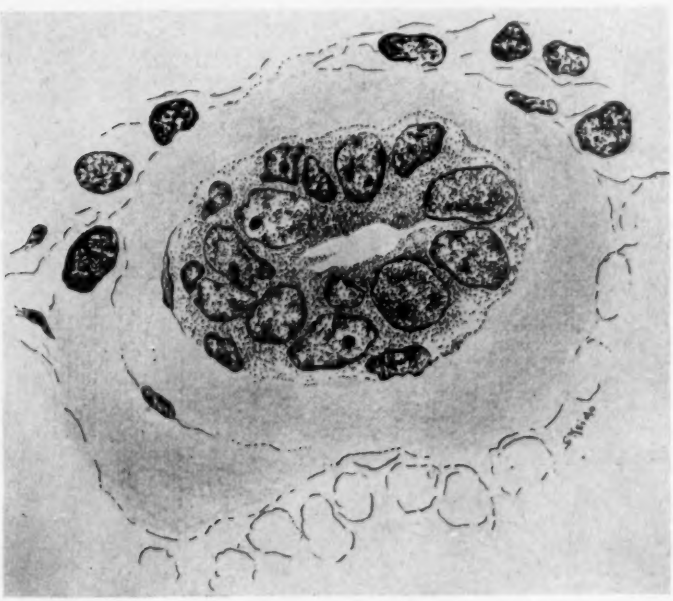

Fig. 4.—Small ducts in a lobule, the main duct of which was filled with carcinoma cells. This ductule shows the earliest changes that could be detected, i. e., commencing hypertrophy of cells and widening of the hyaline band around the ductule.

abnormal for any stage of the sexual cycle. Figure 6 shows a ductule lined by these large cells. The architecture here appeared almost normal; but, owing to the size of the individual elements, no more than four or five surrounded a lumen where normally there would be eight or ten. In most cases, however, the cells had grown at different rates, and the resulting irregularity of size, with compression of some cells, made the abnormality conspicuous (fig. 5). At this stage, the nuclei were often more than twice the normal size. Although many of them were oval as in normal areas, irregularity of contour began to be a marked

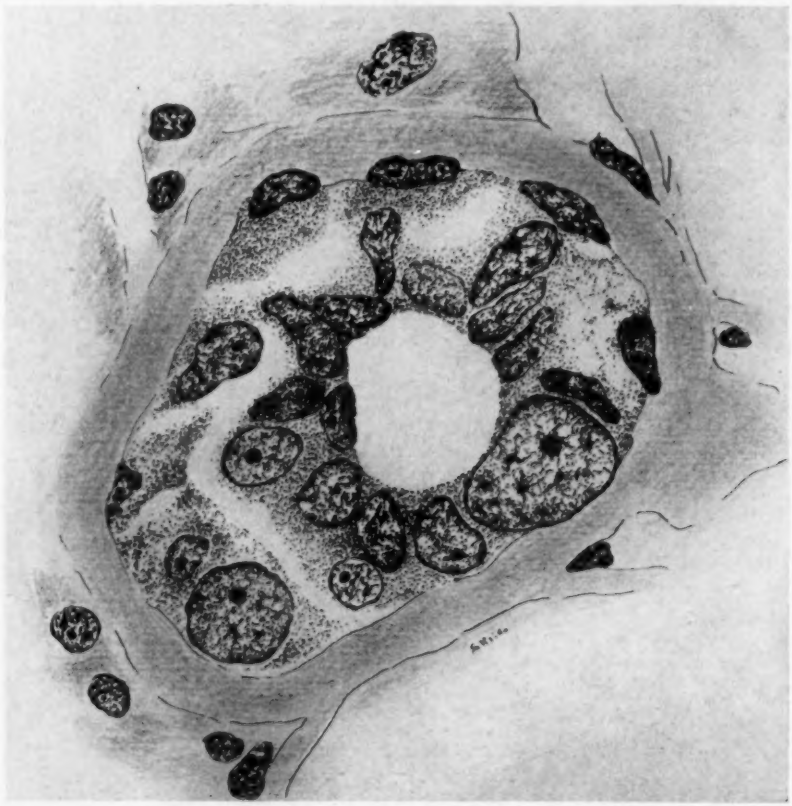

Fig. 5.—An early stage of carcinomatous hypertrophy in a small duct. The ductule was situated in a premenstrual lobule, the main duct of which was the site of malignant growth. The carcinoma in the duct had not reached this part of the lobule, which itself was undergoing malignant proliferation. The drawing shows (1) an irregular overgrowth of the epithelial lining, (2) hypertrophy of the cells of the basement membrane and (3) a wide hyaline band around the ductule.

feature. This, as has been said, may occur in nuclei of premenstrual ductules in noncancerous breasts, but never to the same extent. That the lesion was an overgrowth of preexisting cells seemed to be confirmed by the fact that the spaces in the chromatin meshwork of the nuclei were much larger; i. e., they appeared to be distended by an increase of the colorless material. In some cells,

it looked as though the chromatin threads had given way and retracted, just as elastic fibrils retract when ruptured, and in consequence the nucleus was left stippled with dots of chromatin to which threads were sometimes seen hanging. In the earliest stage, the chromatin seemed to increase in amount with the size of the cell, and it is possible that in some cells this increase continued. But, for the most part, deeply staining tumor cells were seen only where cell division had certainly taken place. As the figures show, abnormal growth was not confined to the lining epithelium, but also affected the cells of the basement membrane. The surrounding hyaline band was now broader; as a rule, it was still present in the next stage.

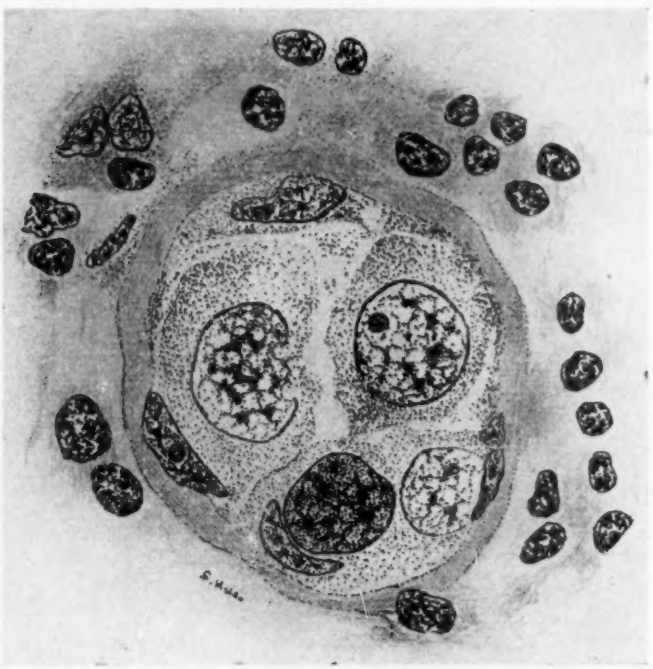

Fig. 6.—A carcinomatous overgrowth of cells in a ductule. The architecture of the ductule is still preserved, but only four cells surround the remains of the lumen. These have reached approximately the limit of their growth. After this stage, they divide or degenerate.

The next phase was that of degeneration or division of the swollen cells, presumably when the cubic contents became too great for the surface area; i. e., when the cell was too large to go on receiving nourishment. In these areas, the normal architecture of the ductules was lost. They became converted into groups of large, irregularly polygonal cells, generally with pale but sometimes dark nuclei; mitoses were numerous.

The carcinoma cells just described arose directly from ductules belonging to lobules that were formed during the course of the sexual cycle. In the larger ducts, a different type of growth was present. The tumor cells were smaller and, if anything, more irregular; they stained more deeply, and the nuclei tended to be elongated, sometimes triangular (this probably represented an attempt at

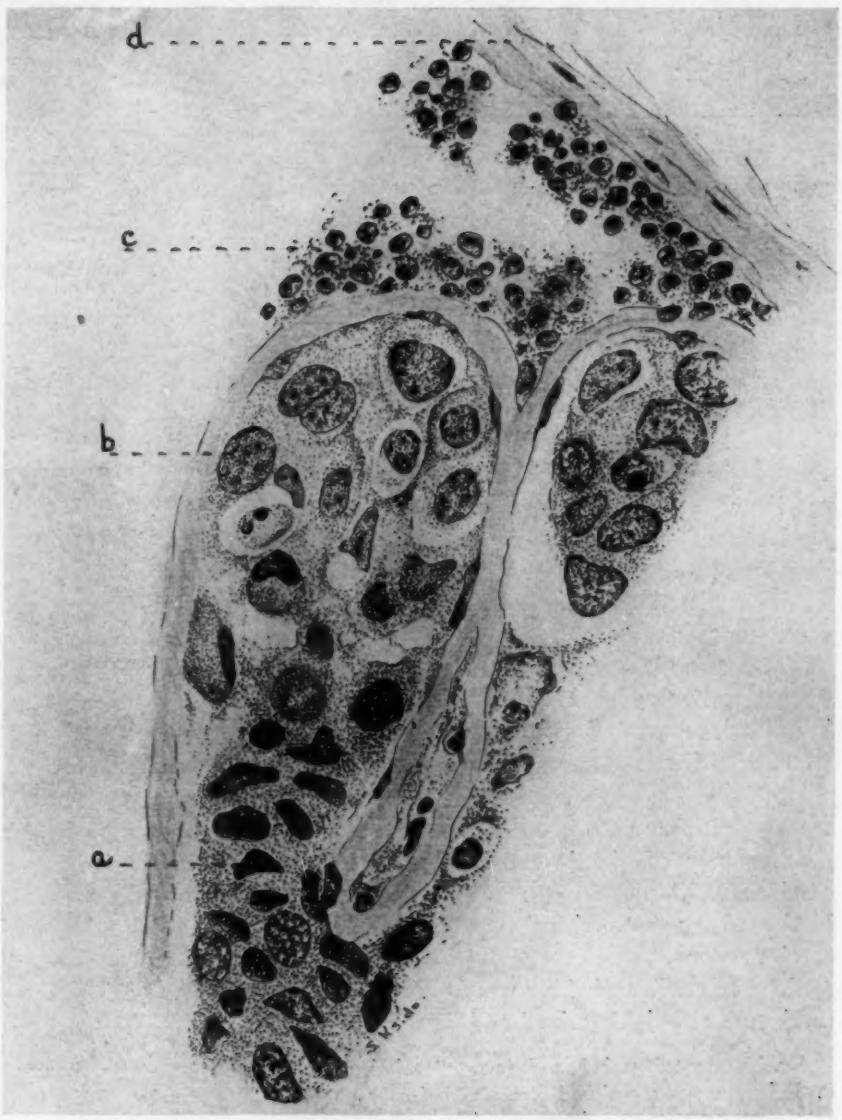

Fig. 7.—The terminal portion of a ductule showing the two varieties of carcinoma cells lying side by side: *a*, carcinoma cells invading a lobule from the main duct; *b*, carcinoma cells arising from the epithelium of the terminal portion of the ductule; *c*, a lymphocytic infiltration, and *d*, outer margin of the lobule. This figure was drawn with camera lucida under 1/12" Zeiss oil immersion; no. 1 eyepiece; tube length, 140 mm.

duct formation). The nuclei showed the remains of a meshwork, but it was irregular and often not present. The change in cell type was evidently the result of rapid, irregular division and of mechanical pressure rather than a fundamental difference. These cells grew centripetally along the ducts, and as the ducts narrowed they became elongated. Finally some of the ductules were invaded by them. The two types of cell then lay side by side (fig. 7).

Comment.—Although one is dealing here with a transformation of cells of lobules into carcinoma, the primary lesion was certainly in the ducts. Wherever the lobule was affected by carcinoma, the duct leading to it was seen to be full of carcinoma cells. The lesion was evidently spreading from ducts to lobules. Figure 2 shows this in almost diagrammatic fashion. The growth of carcinoma cells in the ducts did not quite keep up with premenstrual proliferation, but the lobules had caught the infection, if one may put it that way, or better, were stimulated to undergo malignant changes.

The difference in cell type in the ducts and lobules may be due to the difference in origin of the cells or to the fact that the more carcinoma cells divide, the more atypical they become. The latter explanation is probably correct, for it is to be expected that the duct cells, which had been dividing for some time, would be more undifferentiated than the lobule cells, which were only just becoming carcinomatous.

This case gives some indication of the mode of spread of malignant disease and suggests that the varied appearances presented by the cells in different parts of the same tumor may be an expression of the effect of the menstrual cycle on the growth of carcinoma in the breast.

SUMMARY

A tumor of the breast is described in which two varieties of carcinoma cells are found: (1) cells of the primary growth situated in the ducts; (2) epithelial cells of the lobules, which have become carcinomatous.

The transition of the normal cells of the ductules (and acini) into carcinoma cells is described and figured.

Dr. Margaret Sturgis has given me permission to publish this case. Dr. Stanley P. Reimann has furnished the photomicrographs and Miss Sophy Ksido the extremely accurate drawings reproduced.

Laboratory Methods and Technical Notes

THE PRESUMPTIVE KAHN PROCEDURE IN SYPHILIS BASED ON 15,000 EXAMINATIONS*

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It is known that the presumptive Kahn procedure is capable of detecting smaller amounts of syphilitic reagin than the regular Kahn test.[1] The degree of the greater sensitiveness of this procedure, however, heretofore has not been determined in a large group of cases. From July, 1928, when the Kahn test was made standard in this laboratory, to March, 1929, data have been collected on the sensitiveness of the two procedures. This report gives the results, based on 15,277 examinations in general hospital cases and in 150 cases in which the patients were being treated for syphilis.

Relative Sensitiveness of Presumptive and Regular Tests in Hospital Cases in General.—The Kahn test is performed on the blood of all patients admitted to this hospital. Two methods are employed as a routine in examining each specimen, the regular or conservative method and the more sensitive presumptive procedure. For patients being treated for syphilis, the quantitative Kahn test is also employed.

Table 1 illustrates the increase in sensitiveness of the presumptive procedure over the regular in 15,277 examinations. Of 1,288 serums giving ++++ or +++ reactions with the presumptive procedure, only 878 gave similar reactions with the regular test; of the remaining number, 173 gave ++ or + reactions, 75 ± reactions and 162 negative reactions. Of 181 serums giving ++ or + reactions with the presumptive procedure, 20 gave ++++ or +++ reactions with the regular test, 5 ++ or + reactions, 8 ± reactions and 148 negative reactions. Of 197 serums that gave ± reactions with the presumptive procedure, 3 gave ++++ or +++ , 1 ++ or +, and 193 negative reactions with the regular procedure. The presumptive procedure was negative with 13,611 serums; the regular test gave a strongly positive reaction with 1 of these serums, and was negative with the remaining 13,610 serums.

In considering the totals and the percentages of the various reactions obtained in the 15,277 examinations, I find that of the 1,288 serums that were ++++ or +++ with the presumptive procedure, 902 gave similar reactions with the regular test, so that a 2.5 per cent increase in sensitiveness was shown for the presumptive procedure. Of the + + or + reactions, a percentage of 1.2 was obtained with both methods. The presumptive procedure gave 197 ± reactions, or 1.3 per cent, and the regular test 83, or 0.5 per cent.

* Submitted for publication, June 6, 1929.

* From the Serological Laboratory, University Hospital, University of Michigan.

1. Kahn, R. L.: The Kahn Test, A Practical Guide, Baltimore, Williams and Wilkins Company, 1928, p. 141.

Increase in Sensitiveness of Presumptive over Regular Test in the Case of Patients Being Treated for Syphilis.—The aforementioned groups representing largely diagnostic cases, it was desired to determine the extent of the increased sensitiveness of the presumptive procedure in a group of cases in which the patients were undergoing antisyphilitic

TABLE 1.—*The Increase in Sensitiveness of the Presumptive Kahn Procedure Over the Regular Test with 15,277 Serums*

The Reactions Obtained With			
Presumptive Procedure		Regular Test	
1,288	++++ or +++*	878	++++ or +++
		173	++ or +
		75	±
		162	0
181	++ or +	20	++++ or +++
		5	++ or +
		8	±
		148	0
197	±	3	++++ or +++
		1	++ or +
		...	±
		193	0
13,611	0	1	++++ or +++
		...	++ or +
		...	±
		13,610	0

Totals and Percentages								
	++++ or +++	Per Cent	++ or +	Per Cent	±	Per Cent	0	Per Cent
Presumptive procedure.....	1,288	8.4	181	1.2	197	1.3	13,611	89.1
Regular test.....	902	5.9	179	1.2	83	0.5	14,113	92.4

* ++++ or +++ = strong precipitation; ++ or + = moderate precipitation; ± = weak or borderline precipitation; 0 = no precipitation.

TABLE 2.—*The Increase in Sensitiveness of the Presumptive Kahn Procedure Over the Regular Test with 150 Serums from Patients Being Treated for Syphilis*

The Reactions Obtained With			
Presumptive Procedure		Regular Test	
118	++++ or +++	75	++++ or +++
		14	++ or +
		8	±
		21	0
10	++ or +	10	0
21	0	21	0

Totals and Percentages						
	++++ or +++	Per Cent	++ or +	Per Cent	0	Per Cent
Presumptive procedure....	118	78.7	10	6.7	22	14.6
Regular test.....	75	50.0	14	9.3	53	35.3

therapy. Table 2 summarizes the results of 150 examinations in comparison with the regular test.

It is seen from this table that of 118 serums that gave ++++ or +++ reactions with the presumptive procedure, 75 gave similar reactions with the regular test, 14 ++ or + reactions, 8 ± reactions and 21 negative reactions. Ten serums that gave ++ or + reactions with the presumptive procedure gave negative reactions with the regular

test. Twenty-one that were negative with the presumptive procedure were also negative with the regular test. The presumptive procedure as compared with the regular test showed an increase of 28.7 per cent in ++++ or +++ reactions. The latter test showed an increase of 2.6 per cent in ++ and + reactions, as compared with the presumptive procedure. The ± reactions are not listed in this comparison because such reactions with the presumptive procedure are reported negative in view of the high sensitiveness of the latter method.

With regard to the specificity of the presumptive procedure, while it is not quite as specific as the regular test, it appears to be practically free from false reactions. During the eight months in which the present data were collected, ten positive reactions in cases which clinicians believed were nonsyphilitic were called to our attention. There may have been still other such reactions of what we have not been informed. However, in consideration of the close contact between the clinical staffs and the laboratories, one cannot doubt that the incidence of false positive reactions in the presumptive procedure is small.

With the increased use of the Kahn test as the standard method in the serologic diagnosis of syphilis, there will undoubtedly follow a wider use of the presumptive procedure as a supplementary method. The main value of the latter lies in the fact that it serves as a technical check on the regular test, two methods being more dependable than one. The increased sensitiveness of the presumptive procedure strengthens the diagnostic value of the doubtful or borderline reactions of the regular test, and also, in giving a positive reaction in the face of a negative reaction with the regular test, serves as a stimulus to clinicians to search for evidence of syphilis.

It is of interest to mention in this connection that at the international conference on the serologic diagnosis of syphilis held under the auspices of the League of Nations Health Committee, it was recommended that two methods be employed in the serologic diagnosis of syphilis.[2] The use of the regular and the presumptive Kahn procedures conforms to this recommendation.

SUMMARY

A study was made of the sensitiveness of the presumptive procedure in comparison with the regular Kahn test, based on 15,277 examinations. It was found that in the general run of hospital cases the presumptive procedure was positive in 2.5 per cent more cases than the regular test. In a group of 150 cases in which the patients were being treated for syphilis, this procedure was positive in 26 per cent more cases than the regular test. In view of the fact that the number of false positive reactions obtained with the presumptive procedure is relatively small, the increase in sensitiveness of this procedure over the regular test renders it an important supplementary method in the Kahn reaction.

2. Report of the Second Laboratory Conference on Sero-Diagnosis of Syphilis, League of Nations, Health Organization, 1928, p. 12.

General Review

THE ASCHOFF NODULE *

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So much diagnostic emphasis has been placed by pathologists and clinicians on the presence or absence of the Aschoff bodies in the myocardium in cases of cardiac failure that it seems important to consider what is meant by Aschoff nodules. The expression "typical Aschoff nodule" is often found, but it has been the experience of workers studying myocarditis that the literature has been somewhat indefinite in stating what a typical Aschoff body is.

In this review, I have tried to correlate the descriptions of the Aschoff bodies (as they occur in man and as they are produced experimentally in animals) as given by the different observers and to compare their observations, with what I have seen in a study of fifty cases of acute rheumatic endocarditis in the necropsy material at the University of Minnesota and in a study of experimental rheumatic nodules. The question may be raised as to whether what is called the Aschoff nodule is a specific anatomic lesion like the tubercle or the gumma, or whether it is a more or less nodular area of proliferative or exudative inflammation.

RHEUMATIC NODULES AS OBSERVED IN VARIOUS TISSUES IN MAN

Rheumatic inflammation, either in the form of nodules or in that of irregular groups of large cells, has been described as occurring in the subcutaneous tissues, the joints, the tendons, the galea aponeurotica, the diaphragm, the tongue and other muscles, the tonsils, the arteries and the valves, auricles and ventricles of the heart.

Subcutaneous Rheumatic Nodules.—The subcutaneous rheumatic nodule is found in the loose connective tissues beneath the skin in many cases of acute rheumatic fever. Apparently, the first written account of these nodules was that given by Hillier [1] in 1868. In 1875, Meynet [2] pointed out that these nodular areas bore a direct relation to rheumatic

* Submitted for publication, Nov. 14, 1928.

1. Hillier: Diseases of Children, Philadelphia, 1868; cited by Jacki, E.: Frankfurt Ztschr. f. Path. **22**:82, 1919-1920.

2. Meynet, P.: Rheumatisme articulaire subaigu avec production de tumerues multiple, Lyon méd. **19**:495, 1875.

fever. According to Angel Money,[3] the nodules are less frequent in the acute cases than in the chronic. Cheadle[4] seldom found them in acute rheumatic fever, except in childhood.

The first microscopic description of the subcutaneous nodule was that given by Hirschsprung[5] in 1881. He observed that it consisted of different modifications of connective tissue cells varying in size and shape. Some of the cells were spindle-shaped and others were irregular. They each contained one or more vesicular nuclei, which were larger than those found in ordinary granulation tissue, and the ground substance between the cells was homogeneous. There was an increase in the number of blood vessels within the inflammatory area, and the nodule resembled the tubercle in structure without having its typical appearance. He considered the nodule to be a localized area of inflammation with a tendency to undergo necrosis. In 1881, Barlow and Warner[6] described the subcutaneous nodule as a reaction similar to that found in the valves in acute rheumatic endocarditis. The same observation was recently made by Swift[7] and by Clawson and Bell.[8]

Cavafy,[9] in 1883, called attention to the presence of proliferative endarteritis in these nodules. The proliferating intima sometimes completely closed the lumina of the vessels.

The subcutaneous nodules were found by Futcher[10] to consist of fibrous tissues in various stages of development and the cellular element to be made up of small round cells, fibroblasts and polymorphonuclear leukocytes. Giant cells were also present, some of which contained as many as twenty-six nuclei. Nodules of various stages of development were observed in the same individual. Some nodules had become calcified.

In 1912, Frank[11] described the nodules as being divided into central and peripheral portions. The central area was a homogeneous mass

3. Money, Angel: Surface and Subsurface Nodular Rheumatism, Lancet **1**:540, 1891.

4. Cheadle, W. M.: Harveian Lectures: On the Various Manifestations of the Rheumatic State in Childhood and Early Life, Lancet **1**:871, 1889.

5. Hirschsprung: Jahrb. f. Kinderh., 1881; cited by Frank, P.: Berl. klin. Wchnschr. **49**:1358, 1912.

6. Barlow, T., and Warner, F.: On Subcutaneous Nodules, Tr. Seventh Internat. Med. Cong. London **4**:116, 1881.

7. Swift, H. F.: Pathogenesis of Rheumatism, J. Exper. Med. **39**:497, 1924.

8. Clawson, B. J., and Bell, E. T.: Valvular Diseases of the Heart, Am J. Path. **2**:193, 1926.

9. Cavafy: Rheumatic Nodules, Brit. M. J. **1**:622, 1883.

10. Futcher, T. B.: A Study of Subcutaneous Fibroid Nodules, Bull. Johns Hopkins Hosp. **6**:133, 1895.

11. Frank, P.: Ueber den Rheumatismus nodosus mit besonderer Berüchsightigung des pathologischanatomischen Befundes, Berl. klin. Wchnschr. **49**:1358, 1912.

that stained intensely red with eosin. On special staining, he decided that this homogeneous material was fibrin. The periphery consisted of proliferating connective tissue, which appeared partly as spindle cells and partly as epithelioid cells. Scattered among the proliferating cells often were numerous leukocytes. A variation in structure was noted in different nodules. This variation Frank considered as due to the nodules being at different stages of development. He thought that the primary reaction in the nodule was an exudation of polymorphonuclear leukocytes, and that this was followed by a wandering in of round cells and by a proliferation of the surrounding connective tissue.

According to Swift,[7] the subcutaneous nodules were made up of a conglomerate number of smaller nodules and appeared similar in structure to the nodules found in the heart and other parts of the body. He observed that the center consisted of necrotic material and a small amount of fibrin.

The nodule that I studied was removed from the subcutaneous tissue of a patient with acute rheumatic fever. On microscopic examination of serial sections of the entire gross nodule, I found it made up of many smaller nodular areas of inflammation. The reaction observed was chiefly proliferative, but in many parts polymorphonuclear leukocytes, lymphocytes and what appeared to be fibrin were noted. The proliferative cells varied in size, in shape and in staining qualities. Some of the nuclei were vesicular and some were hyperchromatic. The cytoplasm also varied in the degree to which it took the basic stains. Many of these calls were multinucleated. Some of the nodular areas showed more or less necrosis in the centers. There was an increase in the number of blood vessels, and proliferative endarteritis was noted in the smaller vessels. Morphologically, the reaction observed in this nodule was similar to that described by Hirschsprung,[5] Futcher,[10] Frank [11] and others.

Summary: There seems to be a general agreement by observers who have studied the subcutaneous rheumatic nodules that they consist of proliferating connective tissue cells and a cellular exudate of lymphocytes, plasma cells and polymorphonuclear leukocytes in varying numbers; and that in the center of most of the nodules there is a greater or less amount of homogeneous substance consisting of necrotic material and fibrin.

Rheumatic Nodules in the Galea Aponeurotica.—The rheumatic nodules in the galea aponeurotica of a child 10 years old were studied by Tilph.[12] On microscopic examination, he found them divided each into a central and a peripheral portion. The center contained a mass

12. Tilph: Nodi rheumatici galeae aponeuroticae, Verhandl. deutsch. path. Gesellsch. **17**:469, 1914.

free from nuclei and composed of a material partly fibrillar and partly serous. In the peripheral part were irregular spindle-shaped, multinucleated cells. The multinucleated cells resembled those found in lymphogranulomas. He concluded that the nodules found in the galea aponeurotica were like those in the subcutaneous tissues described by Frank [11] and those in the myocardium described by Aschoff.[13]

The rheumatic nodules in the galea aponeurotica in the cases of acute rheumatic fever described by Jacki [14] did not differ essentially from those in other parts of the body. As seen microscopically, the structure consisted of a proliferative process with some exudation. Giant cells of the Sternberg type with from two to sixteen nuclei were seen. She thought that, genetically and morphologically, the nodules in the galea aponeurotica were similar to the Aschoff bodies in the heart of the same patient and that the small difference that at times was observed could be accounted for on the basis of the different ground substances in which the nodules developed and the different stages of their development.

Rheumatic Nodules in the Joints.—Lesions in the joints with a reaction resembling that found in the nodules in the subcutaneous tissues, in the galea aponeurotica and in the heart were described by Fahr,[15] Swift [7] and Graff.[16] The lesions in the joints examined by Fahr [15] in typical cases of acute rheumatic arthritis did not have the giant cells. He considered the anatomic differences between the inflammation in the joints and the nodules in other parts of the body to be a quantitative one and thought that this quantitative difference might be due to the duration of the action of the virus. He also found that nodules in places other than the heart tended to show a greater degree of necrosis. Swift [17] stated that the variation in other focal lesions from the picture of the Aschoff body in the heart was explained by the difference of the tissues involved and the presence of a superimposed exudative process. Graff [16] was convinced that in the joints and their surrounding tissues the reaction, though less nodular, was as specific as the nodules.

13. Aschoff, L.: Zur Myocarditisfrage, Verhandl. d. deutsch. path. Gesellsch. **8**:46, 1904.

14. Jacki, Elizabeth: Ueber rheumatische Knötchen in der Galea aponeurotica und ihre histologische Uebereinstimmung mit den Aschoffschen Myokardiknötschen, Frankfurt. Ztschr. f. Path. **22**:82, 1919-1920.

15. Fahr, T.: Beiträge zur Frage der Herze und Gelenkveränderungen bei Gelenkrheumatismus und Scharlach, Virchows Arch. f. path. Anat. **232**:134, 1921.

16. Graff, S.: Zur pathologischen Anatomie und Pathogenese des Rheumatismus infectiosus, Deutsche med. Wchnschr. **53**:708, 1927; München. med. Wchnschr. **74**:473, 1927.

17. Swift, H. F.: Rheumatic Fever, Am. J. M. Sc. **170**:631, 1925.

He found in the joints nodular areas that were as characteristic as those found in the subcutaneous tissues or in the heart.

Nodular areas with a proliferative and exudative reaction were found by Graff [16] and others in cases of acute rheumatic fever in the diaphragm, the tongue and other muscles, the tendons, the fasciae and the tonsils. Maclachlan [18] found granuloma-like lesions in the tonsils from rheumatic patients.

Rheumatic Nodules in the Arteries.—Portions of the arterial system, according to Klotz,[19] were as frequently attacked in rheumatism as the musculature of the heart. In a series of arteries studied by him in cases of acute rheumatic fever, he found the inflammatory lesions limited to the adventitia and the media. The lesion consisted of an exudate along the smaller nutrient vessels. This exudate was composed chiefly of lymphocytes and plasma cells, but polymorphonuclear leukocytes sometimes were present in large numbers. The exudative reaction was accompanied with a destruction of muscle and elastic connective tissue.

Pappenheimer and von Glahn,[20] in a comparative study of the aorta in seventy-six cases of acute rheumatic fever and seventy-seven cases in which death resulted from nonrheumatic causes, described what they considered a distinctive lesion of the arteries in many of the rheumatic cases. The lesion was a scar in the region of the nutrient vessels in the media, often acellular, but large mononuclear and multinucleated cells were in some cases arranged irregularly or in nodules in the adventitia. This type of lesion was found in only one of the seventy-seven cases of nonrheumatic diseases. In this case, the patient died with pneumococcic meningitis. Aschoff bodies were present in the heart. In a later study of the aorta in a case of acute rheumatic fever, the large multinucleated cells were found in the media, as well as in the adventitia.

The effect of rheumatic infection on the smaller vessels in various parts of the body was also studied by von Glahn and Pappenheimer.[20] In a study of forty-seven cases, they found what they considered to be a specific lesion in ten cases. The endothelium became swollen and basophilic, and sometimes it was raised from its basement membrane

18. Maclachlan, W. W. G., and Wayne, G. R.: Histopathology of the tonsil in Acute Rheumatic Fever, Arch. Int. Med. **1**:506 (Jan.) 1928.

19. Klotz, A.: Rheumatic Fever and the Arteries, Tr. A. Am. Phys. **17**:181, 1912; Arterial Lesions Associated with Rheumatic Fever, J. Path. & Bact. **18**:259, 1913.

20. Pappenheimer, A. M., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, J. M. Research **44**:489, 1924; A Case of Rheumatic Aortitis with Early Lesions in the Media, Am. J. Path. **2**:15, 1926; Specific Lesions of the Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235, 1926.

by a coagulated exudate. The vessel wall was thickened from a fibrinous exudate. Evidence of necrosis was present in all parts of the wall. Red cells could be seen either immediately beneath the endothelium or in the meshes of the fibrin. Exterior to the necrotic wall there was a cellular exudate, many cells of which were polymorphonuclear leukocytes showing various stages of necrosis. There were also cells with large vesicular nuclei, plasma cells, eosinophils, young connective tissue cells and branching or polygonous mononuclear or multinucleated cells with deeply staining nuclei.

Chiari,[21] studying the vessels in seven cases of acute rheumatic fever, noted diffuse and nodular proliferative inflammation in the adventitia. The nodules showed a cellular reaction not unlike the reaction in the Aschoff nodules.

In a study of the pulmonary artery in twenty-two cases of acute rheumatic carditis, Krugel and Epstein [22] found, in five, active inflammatory changes, consisting, on the one hand, of diffuse cellular infiltration in the media and the subintimal layers of the media, and, on the other hand, of a focal perivascular involvement of the arteries with a cellular reaction comparable to that in the Aschoff nodules in the myocardium.

Summary: The arterial injury described by Klotz,[19] by Pappenheimer and von Glahn,[20] by Chiari [21] and by Krugel and Epstein [22] showed exudative, proliferative and retrogressive processes. The cellular exudative consisted of plasma cells, lymphocytes, eosinophils and polymorphonuclear leukocytes. There was also the fibrinous exudate, as observed in the subcutaneous rheumatic nodules by Frank [11] and Swift.[7] The proliferative reaction was made up of large and irregular mononuclear and multinucleated cells, apparently like the large cells in rheumatic nodular areas of inflammation in other parts of the body. The retrogressive process was made evident by the necrosis. The necrotic process was emphasized by Fraenkel [23] as characteristic of rheumatic inflammatory areas in the heart, and by Frank [11] as characteristic of subcutaneous rheumatic nodules. The reaction in the arteries in cases of acute rheumatic fever appeared to be the same as that found in other foci of rheumatic inflammation.

Rheumatic Nodules in the Heart.—Greater consideration has been given to rheumatic nodules in the heart than to those in any other part

21. Chiari, H.: Ueber Veränderungen in der Adventitia der Aorta und ihrer Hauptäste im Gefolge von Rheumatismus, Beitr. z. path. Anat. u. z. allg. Path. **80**:337, 1928.

22. Krugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, Arch. Path. **6**:247 (Aug.) 1928

23. Fraenkel, E.: Ueber Myocarditis rheumatica, Beitr. z. path. Anat. u. z. allg. Path. **52**:597, 1912.

of the body. Areas of rheumatic inflammation in the heart are found in the valves, auricles and ventricles.

Valves: Barlow and Warner,[6] in 1882, observed a reaction in the valves in cases of acute rheumatic endocarditis similar to that in rheumatic subcutaneous nodules. The inflammatory process in the valves was considered by Swift[7] to be essentially the same as that found in the nodules in the myocardium. He found typical submiliary nodules in the valves. A microscopic study of the valves in cases of acute rheumatic endocarditis from the material available at the University of Minnesota repeatedly showed nodular inflammatory areas with large irregular mononuclear and multinucleated cells. Such typical cellular inflammatory areas were also commonly seen in the valves in cases of subacute bacterial endocarditis.

Auricles: In many cases of acute rheumatic endocarditis, MacCallum[24] noticed a marked thickening of the wall of the left auricle, which he decided was produced mostly by a new growth and to a less extent by a deposit of fibrin on the surface. The layers of the auricles were spread apart by a fluid and by a great infiltration of wandering cells, most of which were mononuclear, but many of which were polymorphonuclear leukocytes and lymphocytes. Most striking were the Aschoff bodies composed of the characteristic large cells. All modifications of these large cells leading to the giant cells were observed. The large cells were forced into rows by the arrangement of the elastic lamellae, so that the Aschoff bodies had a banded appearance.

Of the thirty-one cases of rheumatic endocarditis examined by von Glahn,[25] nine showed a rheumatic inflammatory involvement of the auricles and a gross thickening of the endocardium. On microscopic examination, he observed an exudate consisting of an accumulation of lymphocytes, many polymorphonuclear leukocytes and a few eosinophils. There were the typical large cells arranged radially around a hyalinized center or in palisades. The radial appearance of the nodule he interpreted as probably being a transverse section of one of the elongated palisades. In some sections, he found cells with indistinct outlines, having compressed, distorted, curved and elongated nuclei. With these indistinct cells there were many polymorphonuclear leukocytes, a few eosinophils, small round cells and an occasional plasma cell. In some cases, the polymorphonuclear leukocytes predominated and tended to obscure all the other elements. Von Glahn concluded that the masses of distorted cells and polymorphonuclear leukocytes constituted a feature as prominent and distinctive as the Aschoff bodies.

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24. MacCallum, W. G.: Rheumatic Lesions of the Left Auricle of the Heart, Bull. Johns Hopkins Hosp. **35**:329, 1924.

25. Von Glahn, W. C.: Auricular Endocarditis of Rheumatic Origin, Am. J. Path. **2**:2, 1926.

In my material, microscopic evidence of infection in the auricles was found almost constantly. The reaction was chiefly proliferative and, in some cases, arranged in nodular forms, but there was a great tendency for the proliferation, as well as the exudation, to have a diffuse arrangement. The type of cells did not differ from that found in the nodules in the subcutaneous tissues, ventricles, etc.

Ventricles: The nodular areas of inflammation have been studied more extensively in the ventricles, especially in the left ventricle, than in any other part of the body. These are the nodules that are regularly called the Aschoff bodies. MacCallum [24] found them located chiefly in the left ventricle near its base posteriorly. According to Thalhimer and Rothschild,[26] they were most frequent in the left ventricle. Coombs [27] noted that they were likely to be found in the subendothelial and subepicardial tissues. It has been my experience that the nodules were as frequent in the apex of the left ventricle as in any other part and that they were less frequent in the right ventricle.

The nodules, according to Aschoff,[13] regularly lie in the immediate vicinity of the small or medium size blood vessels, and often show an immediate involvement of the adventitia or at times the other layers of the vessels. He observed that the cells might extend out from the nodule between the muscle fibers, or the nodules might occur between the muscle fibers without any relation to vessels of noticeable size. Aschoff's observations in regard to the location of these nodules were confirmed by Geipel,[28] Coombs,[27] Bracht and Wächter,[29] Takayasu,[30] Fraenkel,[23] Huzella,[31] Thalhimer and Rothschild,[26] Swift [7] and others. Huzella [31] suggested that the immediate proximity of the nodules to the blood vessels resulted from the resistance that the vessels offered to the extension of the nodule. Swift [7] noted that frequently the inflammatory reaction might extend entirely around the vessel or even push into the lumen. On studying serial sections, I commonly found the nodule

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26. Thalhimer, W., and Rothschild, M. A.: On the Significance of the Submiliary Myocardial Nodules of Aschoff in Rheumatic Fever, J. Exper. Med. **19**: 417, 1914.

27. Coombs, C.: Myocardial Lesions of the Rheumatic Infection, Brit. M. J. **2**:1513, 1907.

28. Geipel, P.: Untersuchungen über rheumatische Myokarditis, Deutsches Arch. f. klin. Med. **85**:75, 1905-1906.

29. Bracht, E., and Wächter, A.: Beitrag zur Aetiologie und pathologischen Anatomie der Myocarditis rheumatica, Deutsches Arch. f. klin. Med. **96**:493, 1909.

30. Takayasu, R.: Zur Kenntnis der Sogenannten Endarteritis infectiosa und der Knötchenbildung bei rheumatischer maligner Endokarditis, Deutsches Arch. f. klin. Med. **95**:270, 1909.

31. Huzella, T.: Ueber rheumatische Myokarditis, Virchows Arch. f. path. Anat. **213**:389, 1913; Ueber histologische Befunde bei Rheumatismus und Chorea, Verhandl. d. deutsch. path. Gesellsch. **17**:470, 1914.

surrounding the vessels, especially the smaller ones. In reality, such a condition is an arteritis and corresponds closely to the arteritis observed in the subcutaneous nodules by Cavafy [9] and the arteritis referred to by Klotz [19] and by Pappenheimer and von Glahn.[20] The frequency of this perivascular arrangement of the rheumatic inflammation suggests that the early nodule begins in the small vessels even when the nodule is found in the adventitia of the larger vessels.

The nodule, as first described by Aschoff,[13] was roset or fan-shaped. There was a tendency for it to become elongated and irregular and to extend out between the muscle fibers. As seen by Geipel,[28] the nodules were round, oval or fusiform bodies. In cross-section, they were round or oval. In some of our cases, the nodules confined themselves mainly to the adventitia of the vessels and took on a roset or spindle shape, while in other cases the nodules occurred chiefly in the interstitial tissues away from the larger blood vessels and were fusiform in outline or extended extensively and irregularly throughout interstitial areas of the heart. The inflammation, instead of being arranged in a nodular form, sometimes was so extensive as to appear as a diffuse interstitial myocarditis. This condition was noted by Wätjen [32] and Freund.[33] A diffuse myocarditis was also present in one of the cases described by Geipel.[28]

In my material, marked variations were noted in the size of the nodules. They sometimes consisted of but a few cells near or surrounding blood vessels, and sometimes they were large enough to extend entirely across a section more than a centimeter in width. This I have found in different cases. Nodules were reported by Geipel [28] 1 mm. in length. Fahr [15] described them as 0.8 mm. in diameter. MacCallum [24] was able to see them with the naked eye. It is evident that the nodules are not of uniform size and that they may vary from a few cells to rosets, fusiform bodies or a diffuse myocarditis.

I found that the number of nodules varied greatly in different hearts and in different parts of the same heart. In some cases, several sections had to be examined to find a single nodule, while, in others, the nodules were so numerous that as many as ten could be seen in a single low power microscopic field.

According to the literature, there is a decided variation in the microscopic structure of the nodules. The two chief zones described by Hirschsprung [5] and Frank [11] as occurring in the subcutaneous nodules,

32. Wätjen: Ein besonderer Fall rheumatischer Myokarditis, Verhandl. d. deutsch. path. Gesellsch. **18**:223, 1921.

33. Freund, G.: Zur Kenntnis der acuten diffusen Myocarditis, Berl. klin. Wchnschr. **35**:1077, 1898.

are described as occurring also in the nodules in the heart, i.e., the central and the peripheral zones. The peripheral zone consists in general of a proliferative structure, surrounding the central zone, and an exudative structure, which, as a rule, lies external to the proliferative structure, but the proliferative and exudative cells may be intermixed. As seen by Aschoff,[13] the center of the nodule consisted of a poorly staining or stainless substance that appeared to be a necrotic mass of fused protoplasm. The central necrotic area appeared to him to arise later in the development of the nodule. Geipel [28] studied this necrotic center extensively. He described the hyalinized center as being present in most nodules and noticed that this necrotic material might contract and form a cavity in the center. Thalhimer and Rothschild [26] reported strands in the central mass, which they thought might be fibrin. Contrary to Aschoff, Geipel [28] and Thorel [34] considered the center of the nodule as the earliest stage in its development. According to Pappenheimer and von Glahn,[20] the large cells of the nodules occurred as a result of an injury to primary connective tissue. This is in agreement with Maximow's [35] statement that the polyblasts could assume the forms of giant cells in the presence of foreign bodies. Takayasu,[30] in his study of the nodules, was not able to find the hyalinized necrotic center. The center was described by Coombs [27] as consisting of closely packed large cells. Swift [17] was of the opinion that necrosis was present in the centers of most nodules. In my material, studied in serial sections, many nodules showed the necrotic center, while others showed only the proliferative and exudative reactions.

On the basis of the cellular content, two types of nodules are described: those consisting primarily of large mononuclear or multinucleated cells, and those consisting, for the most part, of large and small lymphocytes, plasma cells, eosinophils and polymorphonuclear leukocytes. Various stages between these two extremes are seen. Occasionally, nodules contain chiefly polymorphonuclear leukocytes and become abscesses. In the description of the nodule, Aschoff [13] referred to the large cell type, and in the illustration in his textbook on pathology he [36] showed the lymphocytic type. He described the cellular zone of the nodule as consisting of large cells each with one or more nuclei, which might be notched or polymorphous. The multinucleated cells he called giant cells, but considered them different from the giant cells found in tuberculosis. They had the appearance of the multinucleated cells found in Hodgkin's disease or of the cells in a sarcoma.

34. Thorel, C.: Pathologie der Kreislauforgane, Ergebn. d. allg. Path. u. path. Anat. **14**:315, 1910.

35. Maximow, A.: Mesenchymal Reactions, Arch. Path. **4**:557 (Oct.) 1927.

36. Aschoff, L.: Pathologische Anatomie **2**:34, 1921.

He stated that the nodules were not composed entirely of the large cells, but had large and small lymphocytes in the periphery between the large cells, or, in some cases, forming an irregular zone of extension out into the connective tissue septums. In these cellular extensions of the nodules, separate large cells could be seen which showed transition forms of the various stages of the large cells.

Both types of nodules were described by Fraenkel.[23] His illustrations showed the nodules to be made up of fusiform bodies consisting almost entirely of more or less spindle-shaped large cells. He described the cellular content of the periphery as being essentially the same as that seen by Aschoff. Geipel,[28] however, laid more stress on the presence of polymorphonuclear leukocytes. He found, in some cases, a rich mixture of these leukocytes. In one of his seven cases there were abscesses as well as Aschoff nodules scattered through the heart. He considered these due to a secondary invasion of staphylococci. In one case, Thalhimer and Rothschild[26] found, associated with the Aschoff bodies in the myocardium, other nodular areas of inflammation identical with those produced experimentally by Bracht and Wächter.[29] This association was interpreted as a rheumatic process with an added bacterial involvement. Such nodules are essentially abscesses. In two of my cases, I found both Aschoff bodies and abscesses in the myocardium. The histories of these two cases follow:

Case 1.—A white boy, aged 9, complained of joint pains, headache, vomiting and difficulty in breathing. His right ankle was swollen and tender for three or four days. After three weeks, he complained of pain in the epigastrium and then in all the joints of the body. Four weeks prior to his admission to the hospital, he was compelled to sleep sitting up because of difficulty in breathing.

Physical examination showed the tonsils enlarged and a definite pericardial rub. The blood showed 5,760,000 red cells per cubic millimeter and a hemoglobin content of 61 per cent. The white cell count was 16,900. The temperature ranged from 99 to 100 F.

The postmortem examination revealed marked edema extending from a point about the level of the umbilicus downward to the ankles. The face showed many purplish areas having the gross appearance of petechiae, particularly around the eyes. Several of these areas were present on the conjunctiva of the lower lid. The two layers of the pericardium were firmly adherent to each other by fibrinous adhesions that were beginning to organize. The heart weighed 165 Gm. It was dilated in both chambers. A large mural thrombus was present in the tip of the right ventricle and also in the right auricular appendage. The mitral leaflets showed numerous pinhead size pearly white nodules along the entire line of contact with the valves. In places, the nodules were present on the chordae tendineae. The aortic cusps had similar vegetations on the ventricular surfaces. Multiple small infarcts were found in the spleen, lungs and both kidneys.

Microscopically, the structure of the nodules and the valves was characteristic of rheumatic valvulitis. On the free edges of the small vegetations, many gram-positive cocci were present, as seen in smears taken from the valve and also in microscopic sections stained by the Gram-Weigert method. On microscopic study

of the myocardium, Aschoff nodules were found, as well as typical abscesses, both often in the same microscopic field. In the abscesses, gram-positive cocci were seen. On the epicardium, cocci in large numbers were present as could be seen in sections stained for bacteria.

CASE 2.—A white man, aged 34, three weeks prior to his death became ill with an acute infection of the maxillary sinus. Ten days before death, he developed a multiple arthritis with a temperature of from 101 to 103 F. He became irrational and restless and died in coma.

The necropsy showed, scattered over the trunk and the neck, numerous small vesicular and hemorrhagic areas. Subpleural petechial hemorrhages were seen over the surfaces of both lungs. The pericardial cavity contained a small amount of thin, cloudy fluid. Scattered over the heart were numerous subepicardial petechial hemorrhages. On the mitral valve along the line of closure were numerous small smooth nodules that, on microscopic examination, showed a typical rheumatic valvulitis. The heart muscle contained both Aschoff nodules and abscesses. In the abscesses, gram-positive cocci were seen. *Streptococcus viridans* in pure culture was grown from the spleen.

The polymorphonuclear leukocytes in the nodules were noted by Bracht and Wächter,[29] who stated that many of the nodules resembled mildly enlarging abscesses. They believed that, in the early stage, the nodules were made up primarily of polymorphonuclear leukocytes and lymphocytes, which later disappeared and were replaced by the proliferative large cells. This conception agrees with what has been found in nodules produced experimentally in animals. Fraenkel [28] also stressed the fact that the large cells were generally mixed with polymorphonuclear leukocytes and lymphocytes and that in many cases the lymphocytic content of the nodule markedly predominated. Illustrations of both types of nodules were given by MacCallum.[37]

It is apparent that there are many variations in the structure of the nodules in the heart, as well as in those in the subcutaneous tissues. These variations might be explained, as suggested by Frank [11] and Fahr,[15] as representing various stages in the development of the nodule. The part of the nodule sectioned, whether periphery or center, also has to be taken into account in interpreting the nodular structure. It would seem that Aschoff's conception that the hyalinized necrotic center occurred in the later stage in the development of the nodule is the more likely, for otherwise this hyalinized center should be found in all nodules. This is found not to be the case when nodules are examined in serial sections.

From the various descriptions, it appears that the periphery of the nodule, in most cases, consists of proliferative large cells, but in many cases, the lymphocytic element predominates. The polymorphonuclear leukocytic content appears to vary. From a study of the literature and

37. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1920, pp. 468 and 572.

my fifty cases, one may come to the conclusion that the nodule may represent any stage from the active acute exudative stage (almost an abscess), which is less common, through the exudative lymphocytic stage to the almost pure proliferative condition, in which the large mononuclear and multinucleated cells are chiefly found.

The origin of the cells in the nodule, especially the large mononuclear and multinuclated cells, is of much interest. The large cells have come to be called the Aschoff cells regardless of whether they are found in the nodules or not. These cells, according to Aschoff,[13] had been described by Hayem and Romberg. Aschoff,[13] in 1904, described the cells as arising from the "lymphocytoiden element" that occurred normally in the tissues surrounding blood vessels and in all inflammatory conditions. In a later discussion, he [36] considered these large cells to be of connective tissue origin.

Geipel [28] was definite in his opinion in regard to the origin of these large proliferating cells. He found that the connective tissue cells became swollen and that the nuclei as well as the protoplasm divided. The cells became multinucleated apparently by cell division or by fusion and formed giant cells, which surrounded the old existing connective tissue cells.

The appearance of these large cells suggested to Coombs [27] that they were the product of connective tissue proliferation in response to an irritant. In the opinion of Huzella,[31] they were composed of swollen connective tissue cells, which finally underwent degeneration. Sacks [38] apparently was convinced that they originated from the histiocytes, although he expressed some doubt concerning the source of these cells. The histiocytes, as shown by Maximow,[35] might originate either from the loose connective tissue cells at the point of injury or from any of the nongranular cells in the blood.

The so-called Aschoff cells described by these authors appear to be the cells called polyblasts by Maximow,[35] who described them as small cells that looked like lymphocytes or as medium size cells that remind one of monocytes or as huge cell bodies with abundant cytoplasm. These polyblasts, he stated, could transform themselves into epithelioid cells of extremely varying aspect and in the presence of foreign bodies could fuse and produce multinucleated giant cells. The large cells in rheumatic infection were called wandering cells by MacCallum and by Thalhimer and Rothschild.

The possibility that these large cells in rheumatic inflammation arose from muscle was suggested by Saigo,[39] Huzella [31] and Whitman and

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38. Sacks, B.: The Pathology of Rheumatic Fever, Am. Heart J. **1**:750, 1925-1926.

39. Saigo, Y.: Dei Purkinjeschen Muskelfasern bei Erkrankung des Myocards, Beitr. z. path. Anat. u. allg. Path. **44**:296, 1908.

Eastlake.[40] In the periphery of the cells in a case reported by Whitman and Eastlake, striae were found that suggested that at least some of the Aschoff cells were derived from muscle fibers. The pathogenesis of these cells was considered a proliferation of the nuclei following degeneration, which might be brought about by the presence of minute infarcts. MacCallum [24] showed definitely that, in the auricles, these cells were not of muscular origin, since they could be found in regions in which muscle did not exist. These are evidently the cells that were called macrophages by Metchnikoff, clasmatocytes by Ranvier, resting wandering cells by Maximow [35] and adventitial cells by Marchand. All these might be included under the term histiocyte. This is the term used by Sacks [38] for the primitive cell from which the Aschoff cell develops. In the opinion of Swift,[7] the large cells arose from the endothelium, but Maximow [35] was not able to demonstrate the development of polyblasts from the endothelium of common blood vessels. It seems evident that, in the rheumatic inflammation, the polyblasts in their various forms are chiefly concerned.

SPECIFICITY OF RHEUMATIC NODULES

The rheumatic nodule in its various forms is generally believed to be a specific type of inflammatory reaction. While Aschoff [13] was not the first to describe the characteristic cell reaction in rheumatic inflammation, he first emphasized the idea that the nodules might represent a specific type of reaction to the rheumatic virus. He studied the nodules in two cases of myocarditis associated with acute rheumatic fever and concluded that such nodules were specific for rheumatic infection. Geipel,[28] Coombs,[27] Fraenkel,[23] Bracht and Wächter,[29] Huzella,[31] Talhimer and Rothschild [26] and others also decided that the nodules were specific for the rheumatic virus. While Fraenkel [23] considered the nodules a specific reaction to the rheumatic infection, he insisted that they were not found in the myocardium in all cases of rheumatic endocarditis. Mönkeberg [41] was not convinced concerning the specific rheumatic etiology of the nodules.

Among the different reasons for the belief in the anatomic specificity of the nodules are the following: The nodules have distinctive histologic characteristics. They are frequently encountered in acute rheumatism; they are infrequently found in other kinds of acute infectious diseases. Nodules similar morphologically and in staining characteristics have not been produced experimentally.

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40. Whitman, R. C., and Eastlake, A. C.: Myocarditis: Histogenic Study of the Type Cells of the Aschoff Body, Arch. Int. Med. **26**:601 (Nov.) 1920.

41. Mönkeberg, J. G.: Herzschwache und plötzlicher Herztod als Folge von Erkrankungen des Atrioventrikularsystems, Ergebn. d. allg. Path. u. path. Anat. **14**:596, 1910.

Distinctive Pathologic Characteristics.—The reaction found in the rheumatic inflammatory lesion is exhibited mainly in the activity of the histiocytes. The same reaction may be seen in different degrees in any subacute or chronic inflammation. The rheumatic inflammation is not a constant type of reaction. There may be nodular and diffuse areas of proliferative inflammation or there may be varying degrees of exudation. The lesion may closely simulate the abscess. Necrosis may be present or absent. The character of the reaction varies in different parts of the body. The reaction may be perivascular, it may involve all the layers of the vessels or it may occur without conspicuous relationship to easily seen vessels. It appears that the inflammation in rheumatism is not necessarily distinctive and that the specificity of the histologic characteristics cannot be considered entirely confirmed.

The Frequency of the Aschoff Nodule in Acute Rheumatic Endocarditis.—It is interesting to consider the constancy with which the Aschoff nodules are found in the heart in cases of endocarditis with acute rheumatic fever. Aschoff [13] found them in both of the two cases of rheumatic endocarditis that he studied. The nodules were present in Geipel's [28] seven cases. In the seven cases studied by Coombs [27] the nodules were present. In seventeen of the twenty cases of rheumatic endocarditis studied microscopically by Fraenkel,[23] nodules were present. Bracht and Wächter [29] observed them in three cases. Takayasu [30] saw Aschoff nodules in a case of what he called malignant rheumatic endocarditis. Huzella [31] studied the myocardium in seven cases of acute rheumatic endocarditis, in all of which the Aschoff nodules were present. He also found them in the heart in two cases of chorea. In one case of rheumatic endocarditis and in two cases of chorea, Douglass [42] found nodules in the heart, which he considered the same as those described by Aschoff and Coombs. Thalhimer and Rothschild [26] examined the myocardium in three cases of acute rheumatic endocarditis and in three cases of chorea and found nodules in all. Tilph [12] found the nodules in one case. Whitman and Eastlake [40] also observed nodules in one case. To 1914, the aforementioned authors examined microscopically the myocardium in sixty cases of acute rheumatism or chorea and on this study based their belief in the specificity of the cellular reaction of the nodules; for, in this series of sixty cases, rheumatic nodules were found in the myocardium in fifty-seven cases (95 per cent).

Since 1914, larger series have been studied with a lower incidence of the nodules. In a study of the heart in fifty-six cases of acute rheumatic endocarditis, Libman [43] noted nodules in eighteen cases (32

42. Douglass, M.: Rheumatic Nodules in the Myocardium, J. Path. & Bact. **18**:119, 1913.

43. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.

per cent). Thayer [44] examined twenty-four hearts. The nodules were present in twenty-one (87.5 per cent). In my series of fifty cases, the nodules were observed in thirty-one (61 per cent). These reports altogether represent 190 cases either of acute rheumatism or of chorea in which search was made for the Aschoff nodules in the myocardium. The nodules were present in 128 (67 per cent). The fact that the Aschoff bodies were absent in such a high percentage of cases of rheumatic endocarditis coming to necropsy again suggests that what is called the Aschoff body in the heart may not necessarily be a specific lesion produced by a specific virus.

Aschoff Bodies in the Myocardium in Nonrheumatic Infectious Diseases.—In cases of typhoid fever, Romberg [45] observed the large type of cell in the interstitial tissues around the blood vessels in the heart. These cells appeared in all respects like those found in cases of acute rheumatic endocarditis by Aschoff and others, but the cells did not appear in nodules. In discussing Coomb's [27] paper on rheumatic myocarditis, Beattie [46] stated that the large cells could be found in nonrheumatic inflammations.

Fahr [15] reported finding proliferative nodular areas in the myocardium in cases of scarlet fever. These nodules had the characteristic location of the Aschoff bodies and the cellular reaction was typical in all respects, except that giant cells were absent. The difference between these nodules and those in acute rheumatic fever seemed to Fahr to be quantitative and to be accounted for by the shorter duration of the process in cases of scarlet fever. Schmorl [47] also found typical rheumatic nodules in the myocardium in a case of scarlet fever. In four of seven cases of scarlet fever, I found nodular areas of proliferation, simulating rheumatic nodules.

In a case associated with pneumonia and possibly produced by the pneumococcus, Pappenheimer and von Glahn [20] found the Aschoff nodules in the myocardium.

The reaction to the syphilitic virus is so similar to rheumatic inflammation that in many cases it is difficult to distinguish between them without the demonstration of the spirochetes in the lesions. In a thorough examination of the myocardium about the aortic ring in fifty cases of syphilitic aortitis, nodular proliferative areas comparable to Aschoff bodies were seen in eight (16 per cent). In some organs with tuberculous infection, the reaction is chiefly proliferative in character.

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44. Thayer, N. S.: Notes on Acute Rheumatic Diseases of the Heart, Bull. Johns Hopkins Hosp. **36**:99, 1925.

45. Romberg, E.: Ueber die Erkrankungen des Herzmuskels bei Typhus abdominalis, Scharlach und Diphtheria, Deutsches Arch. f. klin. Med. **48**:369, 1891.

46. Beattie, J. M.: Discussion of Coomb's paper (footnote 27).

47. Schmorl: Discussion of Huzella's paper (footnote 31).

The proliferative inflammation in the valves in cases of subacute bacterial endocarditis is like that found in the valves in acute rheumatic endocarditis, and the frequency of this similarity seems to be too constant for this inflammation to be considered a separate and distinct associated rheumatic inflammation. Typical nodular areas with giant cells are not infrequently seen in the valves in subacute bacterial endocarditis. Aschoff nodules, when carefully sought, are commonly found in the myocardium in subacute bacterial endocarditis. In twenty-seven (45 per cent) of sixty cases of subacute bacterial endocarditis. Aschoff nodules were found in varying numbers. Many of these were located in partially healed scars. Aschoff nodules or irregular proliferative inflammation or both were noted in 60 per cent of these sixty cases. Various combinations of exudation and proliferation were seen. It was difficult to determine whether some of these areas were abscesses or Aschoff nodules. In some cases, streptococci were found phagocytosed in the large macrophages. As in the valves, this frequency of the presence of the Aschoff bodies and diffuse proliferative inflammation is apparently too great for it to be considered a separate rheumatic infection associated with subacute bacterial endocarditis.

In a case of endocarditis that was shown, by careful checking, to have been produced by the meningococcus, Roads [48] found nodular proliferative areas in the myocardium.

The reaction noted in acute interstitial pneumonia is a proliferative one and, while not in the form of nodules, the cellular reaction resembles that found in the myocardium in acute rheumatic endocarditis. In the inflammation in erysipelas, the cellular reaction consists almost entirely of macrophages. It is worthy of note that the chief cellular reaction to the streptococci is proliferative.

Nodular areas of proliferative inflammation comparable to Aschoff bodies apparently may occur in the myocardium in nonrheumatic infectious diseases, but it is evident that these nodules, except in subacute bacterial endocarditis, are not found nearly as frequently as they are in acute rheumatic fever.

EXPERIMENTAL RHEUMATIC NODULES

In 1909, Coombs, Miller and Kettle [49] injected into rabbits intravenously streptococci recovered from the blood of patients with rheumatic infection and produced arthritis, carditis and other lesions. Many of the lesions in the heart were nodular in arrangement and had a

48. Roads, C. P.: Vegetative Endocarditis Due to the Meningococcus, Am. J. Path. **3**:623, 1927.

49. Coombs, C.; Miller, R., and Kettle, E. H.: The Histology of Experimental Rheumatism, Lancet **2**:1209, 1912.

reaction that was chiefly proliferative. Large cells were found in the nodules, which corresponded morphologically with those found in rheumatic inflammation in man. They decided that the differences existing between the experimental nodular infection and the infection in man could be accounted for by a difference in the mode of entry of the infectious agent in the two conditions.

Bracht and Wächter [29] injected streptococci into two animals and found lesions in the myocardium consisting of muscle destruction with necrosis and exudation. They also noted some diffuse proliferation. The necrotic areas with polymorphonuclear leukocytic exudation are called Bracht-Wächter bodies. Such bodies are not infrequently found in cases of subacute bacterial endocarditis.

By injecting streptococci into rabbits Thalhimer and Rothschild [50] also produced experimental lesions in the myocardium, which corresponded in character to those of Bracht and Wächter. Thalhimer and Rothschild stated that the organisms were not found in the lesions and suggested that the injury and reaction were produced by toxins and not by the bacteria themselves. They considered the lesions to be different from the Aschoff nodules and thought that the only similarity was the occurrence of the lesions in nodules.

Lesions in the interstitial tissues of the heart were produced by Jackson [51] by injecting streptococci into rabbits. These nodular lesions were composed chiefly of large irregular mononuclear and multinucleated cells, which were not different from those found in the heart in cases of rheumatic infection.

By injecting streptococci into the left ventricular cavity of rabbits, I [52] was able to produce nodular proliferative lesions in the myocardium in a high percentage of cases. Microscopically, these lesions showed many multinucleated cells, the cytoplasm of which stained red with methyl-green-pyronin.

In the myocardium of some of the rabbits into which streptococci had been injected, Belk, Jodzis and Fendrick [53] found nodular lesions that they considered similar to the lesions found in the heart in cases of acute rheumatic endocarditis.

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50. Thalhimer, W., and Rothschild, M. A.: Experimental Focalized Myocardial Lesions Produced by Streptococcus Mitis, J. Exper. Med. **19**:429, 1914.

51. Jackson, L.: Experimental "Rheumatic Myocarditis," J. Infec. Dis. **11**: 243, 1912.

52. Clawson, B. J.: Experimental Rheumatoid Myocarditis, Arch. Path. **2**:799 (Dec.) 1926.

53. Belk, W. P.; Jodzis, F. J., and Fendrick, E.: Lesions of Rheumatic Fever Compared with Lesions Produced by Streptococcus Cardio-Arthritidis, Arch. Path. **6**:812 (Nov.) 1928.

Areas of proliferative inflammation, mostly perivascular, were observed by Small [54] in a papule developing at the site of an intradermal injection of a streptococcic vaccine

In a relatively high percentage of rabbits into which had been injected intradermally and subcutaneously strains of streptococci, I [55] was able to produce small nodular proliferative lesions that were, in most cases, entirely similar, in the character of the cellular reaction, to the subcutaneous nodules found in rheumatic inflammation in man.

It is evident that lesions closely simulating those found in the heart and subcutaneous tissues in cases of rheumatic inflammation in man can be produced experimentally in rabbits by the injection of streptococci.

COMMENT

The rheumatic nodule is usually a fairly well localized area of inflammation, which has a more or less general distribution, but which is particularly prominent in the heart and subcutaneous tissues. It is not infrequently found in the joints, tendons, galea aponeurotica, diaphragm, tongue and other muscles, arteries, tonsils, etc. In the heart the most common location is the left ventricle, especially at its base and apex; but the right ventricle and auricles may also be involved. The reaction in the valves is similar to the reaction in the ventricles, but tends to be more diffuse.

The shape of the rheumatic nodule shows a great variation. There may be a few cells partially or completely surrounding the small blood vessels. The nodule may take the form of a roset or become more or less fan-shaped or fusiform. It may extend out irregularly into the interstitial tissues between muscle fibers and become greatly elongated, or, at times, the inflammation may be so extensive as to form a diffuse myocarditis. The tendency to form well defined nodules is greatest in the heart and subcutaneous tissues, but even in these locations diffuse and irregular involvement is not infrequent.

There is no regularity of size. The nodule may be composed of a few cells or it may be large enough to be seen with the naked eye. The number of nodules also varies from only one in many sections to so many as almost to replace other structures entirely.

Frequently, but not always, the nodule is made up of two zones, i.e., a central area and a peripheral area. The central zone is composed mostly of necrotic material intermixed with what appears to be fibrin. This central necrotic area is not present in all nodules, as may be ascertained by a study of nodules in serial sections. This suggests that the

54. Small, J. C.: Rheumatic Fever, Am. J. M. Sc. **175**:650, 1928.

55. Clawson, B. J.: Experimental Subcutaneous Rheumatic Nodules, Am. J. Path. **4**:565, 1928.

central necrosis occurs as a later development in the pathogenesis of the nodule. The peripheral zone and the nodules without necrotic centers are composed, for the most part, of large, irregular or small cells containing, one or more vesicular nuclei. The cytoplasm of these cells tends to be basophilic. The cells are commonly called the Aschoff cells. Mixed in with the so-called Aschoff cells may generally be found lymphocytes, plasma cells, eosinophils and from a few to many polymorphonuclear leukocytes. The polymorphonuclear leukocytes may be so numerous as to cause the nodule to simulate closely an abscess and, in some cases, there are typical abscesses in the same myocardium with the Aschoff bodies. There appear to be three extremes in the structure of the nodule: the proliferative nodule, composed chiefly of large, irregular, vesicular, mononuclear and multinucleated calls; the lymphocytic nodule, made up mostly of lymphocytes, and the polymorphonuclear leukocytic nodule, or abscess. In frequency, these seem to occur in the order given. All intermediate stages between these extremes are commonly seen. This cellular reaction occurring in the nodules appears to be the same as that seen in the joints and other parts of the body. Necrosis is more common in the nodule than in the diffuse inflammation. The greater tendency for the inflammation in the heart and the subcutaneous tissues to occur as nodules may possibly be accounted for by the structure of the ground substance in which the nodules occur.

Two theories have been given concerning the origin of the large, irregular, vesicular, mononuclear and multinucleated so-called Aschoff cells. A myogenic origin has been suggested. This theory seems to have little foundation. The second theory is that the Aschoff cells arise from existing connective tissue cells or the histiocytes, whatever their origin may be. A study of the literature and of my material makes an origin according to the second theory seem evident. At least some of the Aschoff cells arise from existing fixed and fully developed connective tissue cells. The Aschoff cell is probably not a specific type of cell called out by the rheumatic virus, but is the same as the polyblast found in any other form of poliferative inflammation.

While the typical nodular area of inflammation is found more commonly associated with acute rheumatic fever than with any other infectious process, it is doubtful whether it should be looked on as a specific anatomic lesion in the sense that the tuberculous or the syphilitic lesion is. The nodules cannot be said to have distinctive histologic characteristics. They are localized areas of proliferative and exudative inflammation, often with central areas of necrosis and with serous and fibrillar exudation. They show a decided variation in structure from a few cells to a diffuse inflammation and a marked variation in the kinds and number of cells composing them. The nodules are not present in all cases of rheumatic fever. They are frequently found in cases of

subacute bacterial endocarditis, a disease that is known to be produced by streptococci. Nodules, apparently typical Aschoff bodies, are at times found in nonrheumatic infections, as, for example, scarlet fever and syphilis.

The fact that experimental proliferative areas of inflammation so similar to the rheumatic nodules in rheumatic fever in man have been repeatedly produced in the heart, the subcutaneous tissues and the arteries by the injection of streptococci also suggests some objection to the belief that the Aschoff nodule represents a specific lesion produced by an unknown virus.

In conclusion, it may be said that the rheumatic nodule, called the Aschoff body when seen in the myocardium, is a small, fairly well localized area of inflammation, mostly proliferative, but at times chiefly or entirely exudative. The proliferative part of the nodule is composed of mononuclear and multinucleated cells, which vary in size, in shape and in the degree to which their cytoplasm takes the basic stain. The nuclei of these cells, as a rule, are vesicular in character. The cells appear to be modified polyblasts. The exudate consists mainly of lymphocytes, eosinophils and a varying number of polymorphonuclear leukocytes. An association of the proliferative and exudative reactions in varying degrees and combinations is commonly observed, and at times the nodule may closely simulate the abscess.

SUMMARY

The rheumatic nodule is most prominent in the heart and the subcutaneous tissues, but a similar nodular or diffuse inflammatory reactin is not infrequently found in the joints, the tendons, the galea aponeurotica, the diaphragm, the tongue and other muscles, the arteries, the heart valves in endocarditis and the tonsils.

The nodule may consist of but few cells surrounding small vessels; it may have a roset, fan or fusiform shape, or it may become irregular and so extensive as to form a diffuse interstitial myocarditis.

Often, but not always, the rheumatic nodule has a peripheral zone of proliferative or exudative cells and a central zone of necrosis. The cellular content consists of large mononuclear and multinucleated cells, lymphocytes, plasma cells, eosinophils and, in many cases, from a few to so many polymorphonuclear leukocytes that the nodule resembles an abscess. The large so-called Aschoff cells appear to have their origin from the histiocytes and to be but various forms of polyblasts.

The type of inflammation found in the rheumatic nodule in man cannot be said to be characteristic. In a relatively high percentage of cases of acute rheumatic endocarditis, the Aschoff nodules are not found in the myocardium. They are not infrequently found in the heart in cases of nonrheumatic infectious diseases. Nodular areas with a

cellular content similar morphologically and similar in staining characteristics have frequently been produced experimentally in rabbits by the injection of streptococci.

The rheumatic nodule appears to be a fairly well localized area of inflammation, mostly proliferative in character, but at times chiefly exudative.

It is doubtful whether the Aschoff nodule should definitely be considered a specific lesion resulting from a specific rheumatic virus.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—James C. Small, director of the laboratories of the Philadelphia General Hospital, has resigned to engage in the private practice of medicine.

The Prince of Monaco Prize of the Academy of Medicine in Paris has been awarded to A. Borrell, director of the Institut d'Hygiene in Strasbourg, for his work on the etiology of cancer.

Jean R. Oliver, professor of pathology, Stanford University, has been appointed to the chair of pathology in Long Island Hospital Medical College, succeeding Archibald Murray.

Isabel H. Perry and Adelbert M. Moody have been appointed instructors in pathology in the medical school of the University of California; Zera E. Bolin has been promoted to assistant professor.

Esmond R. Long, professor of pathology, University of Chicago, has been appointed editor of the *Journal of Outdoor Life*, published by the National Tuberculosis Association.

Edward Francis of the Hygienic Laboratory of U. S. Public Health Service has been awarded the degree of Doctor of Laws by Miami University, Oxford Ohio.

Walter T. Harrison, U. S. Public Health Service, is the fifth member of the staff of the Hygienic Laboratory to suffer an attack of undulant fever contracted in the course of work with *Bacillus melitensis*.

Lawrence Parsons has been appointed instructor and Joseph C. Vintez demonstrator in pathology in the University of Southern California.

A chair of public health and hygiene has been established in the University of Virginia, and Kenneth F. Marcy of the U. S. Public Health Service has been appointed the first incumbent.

Claribel Cone, Baltimore, at one time professor of pathology in the Woman's Medical College, Baltimore, and well known art connoisseur, has died.

The death is reported of Benjamin Meade Bolton, pathologist to St. Joseph's Hospital, Paterson, N. J., at the age of 72. Dr. Bolton was formerly professor of pathology and bacteriology at the University of Missouri and at the St. Louis University.

F. Klopstock has been appointed chief of the division of immunochemistry of Kaiser Wilhelm-Institut für Biochemie in Berlin-Dahlem, Germany.

It is reported that Pierre Marie of the Pasteur Institute in Paris has died at the age of 38 from botulism accidentally acquired while working on the botulinus toxin.

William G. Hibbs has resigned as pathologist to the Norwegian-American Hospital in Chicago, and Hamilton R. Fishback has been designated to fill the vacancy.

Committee of U. S. Senate on Cancer Research.—Senator Wesley Jones, chairman of the Senate Commerce Committee and its subcommittee on cancer, has mailed to a number of scientists copies of a hitherto unpublished report by a conference on cancer called by the Public Health Service in April, 1928. In this report it is suggested that the Public Health Service could carry on research on cancer along four lines: statistics, occupational cancer, general biochemistry of the cell and radiation. This report will be discussed at hearings of the cancer subcommittee of the senate which are to be held in order to determine whether the federal government should make special provisions for work on cancer.

Grants-in-Aid Fund of the National Research Council.—The Rockefeller Foundation has made available a limited fund from which the National Research Council can make grants-in-aid of comparatively small amounts to support the research of individual American investigators and of special projects of restricted extent.

This fund will be administered by the council in much the same way that its funds for fellowships are now administered. A special committee has been established, composed of the chairman, the treasurer, the permanent secretary and the chairmen of the seven divisions of science and technology of the council. The committee will hold occasional meetings, beginning approximately October 1, to consider and pass on applications. Such applications should not be for fellowships, honoraria or publication costs, but may include field expenses. They should be made well in advance of the time of the intended use of the funds and should include detailed information as to the special qualifications of the applicant to pursue the investigations for which financial assistance is asked, and a statement of other support received or expected. The committee hopes that the universities and other interested organizations will cooperate with it in the proposed modest assistance of worthy research workers.

Correspondence should be addressed to the Secretary, National Research Council, Washington, D. C.

Obituary

PAUL A. LEWIS, M.D.
1879–1929

Paul A. Lewis was born in Chicago, and took his medical degree at the University of Pennsylvania in 1904. While a medical student, he did advanced work in bacteriology and pathology. On graduation, he became resident in pathology at the Boston City Hospital and then assistant in the Massachusetts State antitoxin laboratory. In the years from 1906 to 1908, he was Austin teaching fellow in pathology at Harvard Medical School. During the next two years, he was assistant in pathology at the Rockefeller Institute in New York. He went from there to Philadelphia as director of the laboratory of the Henry Phipps Institute, later becoming also professor of experimental pathology in the University of Pennsylvania. In 1923, he became connected again with the Rockefeller Institute, this time as associate member attached to the department of animal pathology at Princeton, N. J., where he remained until his death. Dr. Lewis made important contributions to pathology, especially in the experimental field. With John Auer, he showed that acute anaphylactic death in the guinea-pig is caused by asphyxia from muscular spasm of the bronchioles. Working with Simon Flexner, he found that experimental poliomyelitis was inoculable from monkey to monkey indefinitely and caused by a filter-passing virus. At the Phipps Institute, he studied tuberculosis and made experiments with pure-line strains of guinea-pigs, on hereditary factors in the resistance to tuberculous infection. These illustrations of his work indicate his achievements as investigator. His interest in pathogenic viruses led him to volunteer for work on the yellow fever virus in Brazil and there he died an untimely death from yellow fever.

PAUL A. LEWIS, M.D.

1879-1929

Miscellany

REPRODUCTION OF PHOTOMICROGRAPHS

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Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

PAIN DUE TO TEMPORARY OCCLUSION OF THE CORONARY ARTERIES IN DOGS. J. FRANK PEAREY, WALTER S. PRIEST and C. M. VAN ALLEN, Am. Heart J. **4**:390, 1929.

A method is described by which the coronary arteries in dogs may be occluded after the animals have recovered from the anesthesia of the preparatory operation. Sudden occlusion produced acute severe pain in dogs, the pain being continuous during the time of occlusion and ceasing immediately with the cessation of occlusion. The responses were due to real pain and not to cardiocirculatory failure or asphyxia.

PEARL M. ZEEK.

PRODUCTION OF PARTIAL LIVER INSUFFICIENCY IN RABBITS. PHILIP D. MCMASTER and D. R. DRURY, J. Exper. Med. **49**:745, 1929.

A rapid and simple method is described for the production of marked liver insufficiency in rabbits. The necessary operation can be carried out by an unassisted operator in a few minutes. The method should further the study of the physiology of the liver. The changes as concerns blood sugar, urea formation and uric acid metabolism would appear to be the same in the rabbit with hepatic insufficiency as in the dog.

AUTHORS' SUMMARY.

TOTAL SURGICAL REMOVAL OF THE LIVER IN RABBITS. D. R. DRURY, J. Exper. Med. **49**:759, 1929.

A technic is described for the total removal of the liver of the rabbit without resultant circulatory difficulties. The method requires a preliminary operation to induce a development of portal and caval collaterals. Rabbits deprived of the liver in this manner, if given dextrose, live for varying periods up to forty hours. Before death, they show the same disturbances as do hepatectomized dogs. They die early of hypoglycemia, unless provided with sugar.

RELATION OF THE LIVER TO FAT METABOLISM. D. R. DRURY and PHILIP D. MCMASTER, J. Exper. Med. **49**:765, 1929.

Fat combustion is carried on adequately in rabbits deprived of the liver or brought into a condition of extreme liver insufficiency. Even twenty-four hours after hepatectomy, fat combustion goes on as well as in the normal animal. Evidently, the liver plays no essential part in the breaking down of fat.

AUTHORS' SUMMARY.

BIOMETRY OF CALCIUM, INORGANIC PHOSPHORUS, CHOLESTEROL AND LIPOID PHOSPHORUS IN THE BLOOD OF RABBITS. ALVIN R. HARNES, J. Exper. Med. **49**:859, 1929.

Experiments are reported in which it was shown that the calcium, inorganic phosphorus, cholesterol and lecithin in the blood of normal rabbits were influenced by four types of light environment. The results of the experiments seem to warrant the following conclusions: Animals exposed to the ultraviolet light for a brief period each day give results that are diametrically opposite to those given by animals living in total darkness. The results obtained in animals exposed to the Cooper Hewitt light and in those living in the open laboratory are somewhat similar, but occupy a position between those obtained with an environment of darkness and with one of ultraviolet light. Animals do not immediately develop the characteristic effects of a particular environmental condition, but pass through a period of accommodation, which varies somewhat with different environmental conditions.

AUTHOR'S SUMMARY.

THE BLOOD IN OBSTRUCTION OF THE CARDIAC END OF THE STOMACH AND AFTER CLOSED-LOOP OBSTRUCTION OF THE JEJUNUM. RUSSELL L. HADEN and THOMAS G. ORR, J. Exper. Med. **49**:945 and 955, 1929.

The blood and the urine of the dog with experimental dehydration have been compared with the blood and the urine of the dog with obstruction of the cardiac end of the stomach. The average duration of life is slightly longer with dehydration than with obstruction. The urine output per kilogram of body weight is almost twice as great with dehydration as with obstruction. The increase in nonprotein nitrogen and urea nitrogen is much the same in the two conditions, although somewhat more marked with obstruction. The chlorides of the blood are markedly increased with dehydration and slightly decreased with obstruction. The increase in fibrinogen and total protein is twice as great with obstruction as with dehydration. These observations indicate that there must be some factor or factors in addition to dehydration producing the toxemia of cardiac obstruction. The chemical observations in the blood of six dogs each with an obstruction of the upper part of the jejunum resulting from closed loops are reported. The duration of life in dogs with closed loops is less than in those with simple obstruction. All animals show a marked rise in nonprotein nitrogen and urea nitrogen, and a fall in chlorides. Usually the carbon dioxide combining power of the plasma is increased. The observations in closed-loop obstruction are essentially the same as in simple intestinal obstruction.

AUTHORS' SUMMARY.

PHYSIOLOGY AND PATHOLOGY OF RESORPTION OF CRYSTALLOIDS FROM THE PLEURAL CAVITY. J. F. BRODSKY, Ztschr. f. d. ges. exper. Med. **61**:24, 1928.

Potassium ferrocyanide is rapidly resorbed from the pleural cavity of the dog and may be demonstrated in the urine within from five to nine minutes after intrapleural injection. The pathways of resorption were studied by the intravenous injection of formaldehyde containing Fe_2Cl_6, which forms a blue precipitate (Berlin blue) with potassium ferrocyanide. The pleural surfaces were deeply stained, but no Berlin blue was found in the lung tissue proper, showing that resorption from the pleura of potassium ferrocyanide is not accomplished by the blood or lymph channels of the lung. Under physiologic conditions, crystalloids are resorbed by the lymph channels of the mediastinum, which may be regarded as the important drainage system of the pleural cavities. When the lymph channels of the mediastinum are inadequate, resorption may also take place through the lymphatics of the diaphragm, the pericardium, the visceral pleura and, rarely, the parietal pleural.

BALDUIN LUCKE.

EXPERIMENTAL AMYLOIDOSIS. F. R. REUTER, Ztschr. f. d. ges. exper. Med. **61**:347, 1928.

It has been claimed (by Domagk, Jacobs) that amyloid may be experimentally produced within a few minutes after injection of various micro-organisms. Reuter repeated Domagk's experiments, using a series of eighty mice, with negative results. One series of animals received a single intravenous injection of living *Staphylococcus aureus*. Other series received repeated intravenous or intraperitoneal injections of *Staphylococcus aureus* killed by heat; after sensitization, they received an intravenous injection of living *Staphylococcus*. The animals were killed within a few minutes after the injection. No substance resembling amyloid was found.

BALDUIN LUCKE.

EFFECTS OF EXTERNAL CHILLING ON RENAL FUNCTION. G. SCHLOMKA, Ztschr. f. d. ges. exper. Med. **61**:405, 1928.

The experiments were conducted on thirty-seven practically healthy boys and men between the ages of 12 and 30 years. Each was given, to drink, from 50 to

75 cc. of tap-water every ten minutes. The bladder was emptied every half hour. Two or three hours after the beginning of the experiment, venous stasis was induced in the legs by a rubber tourniquet, and the legs were then immersed in iced water, having a mean temperature of 2.5 C., for an average of sixteen minutes. In three fourths of the subjects, the amount of urine decreased about 30 per cent, while its concentration increased. In the urine of about one third of the patients, definite traces of albumin appeared temporarily. Generally, these "chilling reactions" took place after and not during the exposure. Without venous stasis, peripheral chilling had little effect on renal function.

BALDUIN LUCKE.

IS EDEMA THE RESULT OF CAPILLARY SECRETION? G. VON FARKAS, Ztschr. f. d. ges. exper. Med. **62**:35, 1928.

The venous pressure and the osmotic pressure of the blood colloids were determined in a number of edematous, as well as nonedematous, patients. It was found that increase of the venous pressure or decrease of the osmotic pressure of the blood proteins was generally associated with edema. Farkas concludes that cardiac edema is generally produced through a rise in venous pressure, while nephritic (the abstractor believes that this should read nephrotic) edema and cachectic edema are the result of lowered osmotic pressure of the blood colloids. This study emphasizes that disease of the capillary walls is not a primary requisite in the formation of edema.

BALDUIN LUCKE.

RETICULO-ENDOTHELIAL SYSTEM AND CARBOHYDRATE METABOLISM. F. Venulet, Ztschr. f. d. ges. exper. Med. **63**:720, 1928.

Blockage of the reticulo-endothelial system of dogs by means of a colloidal silver preparation (2 per cent collargol solution) leads to a marked hyperglycemia, which continues for several hours. Removal of the spleen, which corresponds to a partial blocking of the reticulo-endothelial system, likewise calls forth hyperglycemia; blockage of splenectomized animals increases the hyperglycemia only to an unimportant degree. After blockage there takes place a pronounced depletion of glycogen in the liver. The hyperglycemia induced by blockage of the reticulo-endothelial system is diminished in direct ratio to the reductions of the glycogen storage through starvation, epinephrine or phlorhizin. The degree of the glycogen storage, therefore, determines the magnitude of the induced hyperglycemia. In dogs treated with insulin prior to the blockage of the reticulo-endothelial system, no hyperglycemia occurs; removal of the thyroid likewise prevents a rise in level of blood sugar. However, if thyroidectomized dogs are fed with thyroid extract, a well marked hyperglycemia follows blockage. The hyperglycemia induced by blockage is associated with an increase of blood calcium and a decrease of potassium; there occurs a simultaneous lowering of the blood alkali reserve. The vegetative nervous system plays a rôle in blockage hyperglycemia.

BALDUIN LUCKE.

ABSORPTION ABILITY (PHAGOCYTIC ABILITY) OF THE SURVIVING LIVER. E. J. STERKIN, Ztschr. f. d. ges. exper. Med. **63**:775, 1928.

The purpose of the experiments was to determine whether the reticulo-endothelial system preserves its phagocytic ability in surviving organs. The animals (dogs) were killed by exsanguination without previous narcosis. The liver (and in some experiments, the spleen) was removed, cannulas were tied into the afferent and efferent vessels and the organ was then perfused with a colloidal silver preparation. The amount of silver was estimated in the perfusate by colorimetric, as well as by analytic, methods.

The distribution of the retained silver was determined by histologic examination. It was found that most of the silver was precipitated on the vessel walls, and little was ingested by the Kupffer cells. From this, the author concluded that the phagocytic ability of the surviving liver differs from that of the organ in the living animal.

BALDUIN LUCKE.

Pathologic Anatomy

TRAUMATIC NECROSIS OF THE SUBCUTANEOUS FAT OF THE NEW-BORN INFANT. LEON DE VEL, Am. J. Dis. Child. **37**:112, 1929.

A case of traumatic necrosis of the subcutaneous fat of the new-born infant is presented, with clinical and histologic observations. The symptomatology, pathology and etiology of the condition are reviewed.

AUTHOR'S SUMMARY.

THE DECIDUAL REACTION IN EXTRA-UTERINE PREGNANCY. B. S. KLINE, Am. J. Obst. & Gynec. **17**:43, 1929.

From a study of seventy-four cases, Kline found evidences supporting the belief that a decidual reaction of a greater or less extent occurs at the site of implantation. The termination of tubal pregnancy by hemorrhage depends on the inability of the scant decidua present to prevent invasion of the trophoblast into the blood vessels. The decidual tissue at the site of implantation persists only as long as the chorionic villi are intact; but that present elsewhere, such as in other portions of the tube and lining the uterus, though not constantly present, may persist after involution of the local decidual tissue has taken place.

A. J. KOBAK.

RELATION OF ECTOPIC GESTATION TO THE ASSOCIATED UTERINE CHANGES AND VAGINAL BLEEDING. SAMUEL H. GEIST and MORRIS R. MATUS, Am. J. Obst. & Gynec. **17**:151, 1929.

Geist and Matus studied thirty-nine cases of ectopic pregnancy in which the endometrial tissue was available for study. From this study uterine bleeding was found to be due to the following causes: (1) trauma, wherein the patient believing herself to have a normal pregnancy has attempted to induce abortion (two cases); (2) casting off of the uterine decidua which is associated with or preceded by bleeding and is initiated by the actual death of chorionic tissue, and (3) spotting, which was probably caused by uterine contractions initiated by efforts of the tube to expel its contents rather than death of the ovum.

A. J. KOBAK.

SPINDLE CELL SARCOMA OF THE KIDNEY IN ADULTS. H. L. KRETSCHMER and H. S. RANDOLPH, Ann. Surg. **88**:1033, 1928.

The case is interesting because of its rarity. In 97,000 autopsies reported by Lubarsch only four instances were found. The case occurred in a man, aged 55, with a large tumor mass in the left kidney weighing 750 Gm., composed of closely packed spindle cells. A brief description of eleven cases from the literature is appended.

N. ENZER.

ADENOCARCINOMA OF THE TESTIS IN THE ADULT. A. R. STEVENS and J. EWING, Ann. Surg. **88**:1074, 1928.

This is a report of a tumor removed from a man 51 years of age, which had a glandular structure due to the arrangement of the cells on a papillary stroma. The tumor grew slowly and metastasized slowly, and the authors hold that it should be differentiated from the embryonal carcinoma.

N. ENZER.

MESENTERIC INJURIES AND INTESTINAL VIABILITY. T. C. BOST, Ann. Surg. **89**:218, 1929.

This is a brief inquiry into the question as to how much intestine may be deprived of its circulation from the mesentery and yet survive. Case reports of three patients are recorded, in whom from 3 to 8 inches (from 7.6 to 20.32 cm.) of mesentery had been torn from the intestinal border. Also, in three dogs 6, 8 and 10 inches (15.24, 20.32 and 25.4 cm.) of mesentery were separated from the intestine. The patients and the dogs recovered after the mesenteric vessels had

been tied; the border of the intestine resutured, and the omentum tacked around the loop. It remains unsettled as to how much vascular recovery takes place through the omentum in these instances. The problem seems to have clinical significance.

N. ENZER.

SUBCUTANEOUS RUPTURE OF THE STOMACH. O. GLASSMAN, Ann. Surg. **89**: 247, 1929.

The author has collected from the literature the reported cases of spontaneous and traumatic rupture. The latter he divides into those resulting from severe trauma and those resulting from moderate or slight trauma. A further group of spontaneous rupture seems to be related closely to those classified under slight trauma. The lacerations vary in size, and in the cases reported an explanation is not forthcoming. The combined effect of undue distention with acute local changes seems to obtain. In the instances of spontaneous rupture, the mechanical effect of acute distention seemed to be insufficient. Some local change, such as acute ulceration, would seem to be necessary. The article is valuable for its appended list of cases and excellent bibliography.

N. ENZER.

MYOMA OF THE APPENDIX. A. R. KOONTZ, Ann. Surg. **89**:272, 1929.

Fourteen cases of myoma of the appendix are tabulated, including the author's. In this instance, the myoma was diffuse in the muscular coat.

N. ENZER.

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX. J. SELINGER, Ann. Surg. **89**:276, 1929.

This review might better be entitled "Carcinoid of the Vermiform Appendix." This term has been applied to the curious tumor of the appendix in preference to the author's title, because it immediately distinguishes it as a nonmalignant one and probably of an entirely different fundamental nature. The author ascribes the first authentic description of this condition to Beeger in 1882. In 1926, about 300 cases had been reported. The author adds thirty-four cases.

N. ENZER.

DIABETES MELLITUS: A STUDY OF ONE HUNDRED AND FORTY-SEVEN AUTOPSIES. WILLIAM F. GIBB, JR., and VICTOR W. LOGAN, Arch. Int. Med. **43**:376, 1929.

A study of 147 cases of diabetes mellitus in which autopsy was performed was made with particular reference to the pathologic structure of the pancreas and the clinical course of the disease. Interstitial pancreatitis was found in 123 cases, 79 of which showed well advanced lesions. While this condition is more frequently present in older persons, it is often found in middle-aged persons. An explanation for this is offered in six cases showing acute inflammation of the interstitial tissue of the pancreas. A direct relation was found between the incidence of interstitial pancreatitis and lesions of the insular tissue (table 2). Tuberculous lesions in the pancreas were not found in any case. Lipomatosis of the pancreas is a late result of atrophy of the acinar tissue due to interstitial pancreatitis. Definite lesions of the islands of Langerhans were found in all but eleven of the cases studied. These lesions varied from difference in the staining reactions of the cells to fibrosis of the islands and hyaline degeneration. One case of calcified islands was seen. No relation was found between the type of cases in which gangrene was present and the degree of damage to the islands. The same is true of coma. An analysis of eleven cases without apparent damage to the islands showed that six patients did not have glycosuria when placed on a diet without insulin. It is hoped that a simple test may be devised to enable one to correlate the severity of the diabetic condition. Until this has been done, it seems impossible to relate the clinical and pathologic observations in diabetes mellitus.

AUTHORS' SUMMARY.

COARCTATION OF THE AORTA: A CASE OF THE ADULT TYPE IN A CHILD SIX MONTHS OF AGE. A. M. SALA and I. NACHAMIE, Arch. Int. Med. **43**:420, 1929.

Coarctation of the aorta may be either "infantile" or "adult." The first term is applied to those cases presenting a diffuse narrowing of the fetal isthmus; the second, to those presenting a relatively abrupt stricture, varying in degree, in the vicinity of the ligamentum arteriosum. A child, 6 months old, who was admitted with a bronchopneumonia of at least two days' duration, died some hours after admission. The developmental and family history was negative, but the infant had been ill with diphtheria and discharged from the hospital as cured eighteen days previous to second admission. No cardiac signs were elicited on examination because of the masking signs of bronchopneumonia. Autopsy revealed, in addition to an extensive bronchopneumonia, a localized necrosis of the left bronchus and a coarctation of the aorta of the "adult" type. This was accompanied by a patent foramen ovale, a moderate dilatation above and below the stricture and a moderate hypertrophy of the left side of the heart.

AUTHORS' SUMMARY.

ALZHEIMER'S DISEASE. WILLIAM MALAMUD and K. LOWENBERG, Arch. Neurol. & Psychiat. **21**:805, 1929.

Alzheimer's disease is considered a form of senility, or rather presenility, as it usually occurs in persons between the ages of 56 and 63. Malamud and Lowenberg report two cases; one patient died at the age of 65 (date of onset four years previously), the other at the age of 23 (duration about nine years). The first case presented a rather typical picture: mental confusion; memory defect; asthenia with inability to work; apraxia; speech disturbances, especially in the form of logoclonia (repetition of words); extreme untidiness, and complete disorientation. In the second case, the symptoms were approximately the same but the speech disturbances were not described, though they were present. The authors themselves doubt whether the second case should be classified as Alzheimer's disease, especially in view of the very young age of the patient and the long remission—four years' duration. However, the pathologic changes were alike in both cases—senile plaques practically all over the cortex, especially in the Ammon's horn but absent, in the first case, in the occipital lobe; so-called Alzheimer's fibrillary changes of the ganglion cells when stained with the method of Bielschowsky; cell destruction in the putamen and marked changes in the choroid plexus (which they classify as primary vascular disease, thrombosis of the capillaries with secondary changes in the form of connective tissue hyalinization and proliferation, and general hyperplastic transformation of the entire organ). The tufts or their cells showed hardly any significant changes. Those that were present were considered by them secondary. In the second case no normal plexus tissue was present. Scarlet red or sudan III have been used only in case 1. In view of the observations in these two cases they are inclined to accept Kraepelin's view that Alzheimer's disease may be independent of the senile group and that it may occur at any age.

G. B. HASSIN.

UNILATERAL NEUROFIBROMATOSIS OF THE CRANIAL AND DEEP CERVICAL NERVES. GEORGE T. PACK, Arch. Neurol. & Psychiat. **21**:919, 1929.

A boy, aged 11, of average intelligence, had an overgrowth of the left side of the face, pain and partial blindness in the left eye and daily vertigo. At the age of 2 months a fixed enlargement of the left pupil appeared, and at the age of 4 months the soft parts of the left side of the face became noticeably enlarged, and progressed gradually during the next ten years. The neurologic examination revealed exophthalmos of the left eye, probably caused by a retrobulbar tumor, and a mild keratoglobus; the left pupil was dilated and fixed; the retina (left?) was undergoing atrophy and the blood vessels were collapsed, except near the disk where they were engorged. The left side of the face was swollen and numerous

discrete, freely movable tumor masses were present in the left upper eyelid, left cheek and the left side of the neck, particularly on the posterior cervical triangle and along the anterior border of the sternocleidomastoid muscle. There was marked asymmetry; the thorax, scapula, pectoral muscles, leg and arm were much smaller on the left side than on the right. Roentgenogram of the skull revealed the left orbit to be smaller than the right and the left antrum "abnormal in size and location." The examination of an excised nodule (from the neck) showed it to be rather avascular, surrounded by a capsule and pierced, as it were, by nerve fibers. The latter were dissociated by the intervening prolongations of the capsules. The major portion of the tumor consisted of fibroblasts, and most of the nerve fibers were deprived of their myelin. Some portions of the tumor mass exhibited mucoid degeneration. It was impossible to ascertain whether or not the connective tissue cells were neuroglia cells from the sheath of Schwann. In some areas, the cells were "in anastomotic chains." The author comments on the possibility of the effect neurofibromatosis may have on the bones, that the bone changes observed in this patient might have been caused by neurofibromatosis.

G. B. HASSIN.

SYNDROME OF TUMOR OF SPINAL CORD DUE TO ADENOCARCINOMA MUCOSUM OF THE PAROTID GLAND WITH GENERAL METASTASIS. J. L. GARVEY, Contributions to Medical Science Dedicated to A. S. Warthin, Ann Arbor, George Wahr, 1927, p. 661.

Garvey records a case of primary adenocarcinoma mucosum of the parotid gland which gave the first evidence of metastasis eight years after operation on the primary neoplasm, when symptoms and signs of localized compression of the spinal cord appeared. Postmortem examination revealed extensive metastasis to the vertebrae, femora, calvarium, sternum, clavicle, lungs, liver, retroperitoneal lymph nodes and suprarenal glands.

WALTER M. SIMPSON.

THE PITUITARY ADAMANTINOMA. M. M. PEET, Contributions to Medical Science Dedicated to A. S. Warthin, Ann Arbor, George Wahr, 1927, p. 673.

Peet describes two cases of adamantinoma of the pituitary region. One, a typical adamantinoma of craniopharyngeal duct origin, was primarily intrasellar, the tumor apparently having its origin in the extreme lower end of the infundibular stalk; the other tumor, an adamantinocarcinoma, arose from the extreme upper end of the infundibulum. A typical Fröhlich syndrome developed in the first case.

WALTER M. SIMPSON.

REACTIONS OF THYROID TO INFECTIONS ELSEWHERE IN THE BODY. WARREN H. COLE and NATHAN A. WOMACK, J. A. M. A. **92**:453, 1929.

In septic and toxic processes there may be hyperplasia, loss of colloid, desquamation and decrease in iodine in the thyroid. Experimental data also support the idea that the thyroid takes an active part in reactions due to infection and toxic action.

GAUCHER'S SPLENOMEGALY. NATHAN ROSENTHAL and B. S. OPPENHEIMER, J. A. M. A. **92**:637, 1929.

Roentgenographic changes in the bones in the course of Gaucher's disease are not uncommon, and are of value in establishing the diagnosis. In six of our eight cases which were examined by the roentgen rays, characteristic bone changes were found. The commonest early change was a fusiform expansion of the lower third of the femurs. Gross skeletal changes, such as gibbus and pathologic fractures, are rare. We have observed only one well marked instance. Gaucher's disease, Niemann-Pick's disease and possibly the infantile form of amaurotic family idiocy (Tay-Sachs) are congenital, familial, constitutional disturbances of lipoid metabolism. Splenectomy in Gaucher's disease cannot be considered a

curative measure. It may, however, be of value in relieving the anemia, the hemorrhagic diathesis or the burden to the patient of the spleen itself.

AUTHORS' SUMMARY.

CALCIFICATION OF THE VESSELS IN DIABETES. L. B. MORRISON and I. K. BOGAN, J. A. M. A. **92**:1424, 1929.

Roentgenographic evidence of calcification of the vessels was present in the legs in 53 per cent of 324 diabetic patients varying in age from 2 to 81 years. In the third decade 6 per cent of the patients showed vascular calcification, and in the seventh decade 87 per cent. Twenty-one per cent showed advanced calcification. Advanced calcification was not found in patients under 40 years of age, although definite calcification was present in five cases. No case of gangrene was found in a patient under 40 years of age. Syphilis, dental infections and arthritis appear to play no part in the production of vascular calcification in this series. Seventeen per cent of patients without calcification (average age, 41 years) and 49 per cent of those with calcification (average age, 59 years) have blood pressure over 150. Patients over 50 years of age with sclerosis are about twice as apt to have high blood pressure as those without calcification. Six, or 9 per cent, of the patients with diabetes of ten years' duration did not show calcification.

AUTHORS' SUMMARY.

EFFECT OF COPPER ON THE LIVER. FREDERICK B. FLINN and WILLIAM C. VON GLAHN, J. Exper. Med. **49**:5, 1929.

Copper, or its compounds used, does not cause the deposition of pigment in the livers of rabbits, guinea-pigs or rats. Neither does it produce a cirrhosis in these animals. Spontaneous deposition of pigment occurs frequently in the livers of normal rabbits on the usual laboratory diet. The feeding of a diet of carrots exclusively will produce deposition of pigment in the livers of rabbits, in every way identical with that ascribed to copper. The pigment deposited in the livers of rabbits is probably of exogenous origin.

AUTHORS' SUMMARY.

THE LYMPHATIC TISSUE. WILLIAM EHRICH, J. Exper. Med. **49**:347 and 361, 1929.

1. *In Subcutaneous Infection with Staphylococci.*—On subcutaneous infection of rabbits with staphylococci of low virulence there appears at the place of injection first a hemorrhagic purulent inflammation and later a localized purulence. In the regional lymph nodes there is lymphatic hyperplasia, and in the blood a lymphocytosis. In the regional lymph nodes there is first a regressive change of Flemming's secondary nodules and of transmission forms. Then follows lymphatic hyperplasia, starting apparently from solid secondary nodules and progressing by way of pseudo-secondary nodules to a diffuse lymphoid hyperplasia. The increase of lymphocytes in the blood parallels this development. Only after the highest point of the lymphocytosis has been reached or passed are the first Flemming's secondary nodules found, which thereafter increase in number and size while the number of lymphocytes in the blood falls, and reach their maximum development when the number of lymphocytes in the blood is again normal. Therefore, the original conception of Flemming that the site of formation of the lymphocytes of the blood is in Flemming's secondary nodules, cannot be accepted. The lymphocytes of the blood originate in the pseudo-secondary nodules as in embryonic life. The mother cells of the lymphocytes would appear to be Marchand's proliferating endothelial (reticular) cells.

2. *After Intravenous Injection of Killed Staphylococci.*—In eighty-seven rabbits, some of which received intravenously at various intervals small doses of killed staphylococci and others large doses, the following observations were obtained. There occurred a hyperplasia of lymph nodes, spleen and thymus, that is to say, a status thymicolymphaticus. This phenomenon is explained as due to immediate

local irritation caused by bacteria and their products and by certain "toxins," partly of exogenous, partly of endogenous origin. The lymphocytosis which appeared was parallel in time and degree with the hyperplasia of the peripheral lymph nodes (axillary, popliteal and cervical lymph nodes) and probably originated in the pseudo-secondary nodules of these nodes. There occurred intense mesenchymal reaction in the vascular connective tissue of the lungs, liver and spleen, and after large doses slighter reactions in the suprarenals, kidneys and heart. These reactions correspond with Oeller's adventitial reactions and Siegmund's intima proliferations. In the interstitial tissue of these organs as well as in the walls of the minor vessels, proliferations of cells, partly of the type of lymphocytes and plasma cells, partly of that of histiocytes and reticulo-endothelial cells, appeared, which, after large doses, were mixed with many giant cells of Langerhans' type. After small doses, lymphocytes and plasma cells predominated; after large doses, histiocytes and reticulo-endothelial cells. Because these reactions occurred immediately after the first injection, they can be regarded as primary reactions of the organism to bacteria and their products.

AUTHOR'S SUMMARY.

CHRONIC NEPHRITIS INDUCED IN THE DOG BY URANIUM NITRATE. WILLIAM DEB. MACNIDER, J. Exper. Med. **49**:387 and 411, 1929.

1. *Functional and Pathologic Study.*—Uranium nitrate in the dog induces an epithelial injury to the kidney which is largely localized to the proximal convoluted tubule epithelium. With the development of such structural changes in this tissue, functional alterations are induced in the glomeruli which later in the experiments are shown structurally by the formation of connective tissue in these units. The evidence of impaired renal function, other than the water elimination by the kidney, progressively increases as the epithelial injury becomes intensified. A certain number of dogs rendered acutely nephritic from uranium, after a variable period allowed for renal repair, returned to a complete functional normal. The commencement of such a restoration in function is coincident with the development of the process of epithelial repair in the injured tubular epithelium and at the same time with the development of histologic evidence of structural changes in the glomeruli. The ability of such animals to effect a restoration in normal renal function depended on the completeness and type of epithelial repair which develops and not with the degree to which connective tissue formation and obliteration of glomeruli have failed to develop. A final group of animals, after having developed acute nephritis, were unable to effect such changes of repair in the kidneys that a normal functional state could be established. These animals showed the anatomic characteristics and the functional expression of a chronic nephritis. Such a failure to return to a state of functional normal has been associated in them with the regeneration in the proximal convoluted tubules of a predominant type of epithelium which is atypical for the tubules in this location and with the development of structural changes in the smaller arteries of the kidney and obliterative changes in the glomeruli. The study as a whole emphasizes the functional value of the proximal convoluted tubule epithelium during periods of acute renal functional depression, when such periods are recuperated from with the establishment of a state of normal renal function, and in conditions in which without a complete restoration of function a functional improvement has developed with the establishment of a chronic nephritis.

2. *Response of Kidney to Second Injection of Uranium Nitrate.*—Uranium nitrate in the dog has a high degree of selective affinity as a nephrotoxic for the epithelium of the proximal convoluted tubules. The glomeruli participate in the injury and develop obliterative connective tissue changes as evidence of a preexisting acute injury followed by repair. The repair to the degenerated tubular epithelium is accomplished by two processes. First, by a regeneration of convoluted tubule cells from such cells not too severely injured in this location. This type of regenerated epithelium has no resistance to uranium. Second, the regeneration may occur as an ingrowth of cells or as syncytial buds from cells in the terminal portion

of the proximal convoluted tubule or from the upper end of the descending limb of Henle's loop. This type of regenerated epithelium which is entirely different cytologically from normal convoluted tubule epithelium is resistant to a second injury from uranium even when the amount of this nephrotoxic agent has been increased to double the amount of the initial injection. The kidney does not develop a local tissue immunity or resistance to uranium in the sense that cells of the same type once injured by it acquire as a result of the injury a resistance. The resistance and apparent but not real immunity is due to another type of cell with resistance having been substituted for a cell with but little resistance. This fact may be looked on as constituting part of a defense mechanism in the kidney and may in part explain the long duration of certain types of chronic nephritic processes. The functional studies which have been made during the initial injury from uranium to the tubules and during the secondary injury in animals which have either shown a resistance or a lack of resistance, emphasize the importance of the tubular epithelium as a part of a secretory mechanism in urine formation. During periods when the proximal convoluted tubule epithelium is in a state of acute degeneration there is a disturbance in the acid-base equilibrium of the blood, a reduction in the elimination of phenolsulphonphthalein and a retention of urea nitrogen, nonprotein nitrogen and creatinine. When this epithelium is regenerated by the formation of a tubular epithelium normal in character for this location of the tubule, regardless of structural changes in the glomeruli, the foregoing evidence of renal dysfunction returns to the normal. If at such a period this type of regenerated epithelium be injured by a secondary injection of uranium a state of acute renal dysfunction is induced in an intensified form. In those animals in which the repair to the tubules was accomplished by the formation of an atypical type of epithelium in the convoluted tubules as well as by the formation of cells normal in histologic appearance for this part of the tubule there was an improvement in the degree of depletion of the reserve alkali of the blood, in the elimination of phenolsulphonphthalein and in the retention of urea nitrogen, nonprotein nitrogen and creatinine. Certain of these values did not reach the normal. In such a state of renal repair when a second injection of uranium was given the kidney was found to have developed a marked resistance to it. There was but slight evidence of a depression in renal function. Associated with this acquired functional resistance there was no evidence of injury to the atypical, flattened regenerated epithelium of the proximal convoluted tubules.

AUTHOR'S SUMMARY.

OBSTRUCTION TO CARDIAC CORONARY SINUS. R. T. GRANT and T. DUCKETT JONES, Heart **14**:241, 1928.

One case is described in which the coronary sinus was occluded by a fibrous diaphragm apparently not due to a congenital malformation but to an old thrombus.

AUTHORS' SUMMARY.

HEART VALVE IRREGULARITIES IN RELATION TO SUBACUTE BACTERIAL ENDOCARDITIS. R. T. GRANT, J. EDWIN WOOD, JR., and T. DUCKETT JONES, Heart **14**:247, 1928.

Recesses, pockets, crevices and projections related to heart valves do not, in themselves, afford a foothold for bacteria. Degenerative changes in heart valves often lead to the deposition of small platelet thrombi on the surface and these thrombi offer passing organisms a nidus for their establishment. Therefore, if organisms invade the blood stream at a time when a thrombus is forming on a heart valve, the conditions are suitable for the development of bacterial endocarditis.

PEARL ZEEK.

CHRONIC APPENDICITIS. T. BHASKARA MENON, Indian J. M. Research **16**:656 and 661, 1929.

1. *The Lymphoid Tissue of the Appendix.*—A cross-section of a normal appendix shows on an average about six lymph follicles and three well defined

germ centers. In a chronically inflamed organ there is a tendency for atrophy of the lymphoid tissue to occur. Lymphoid cells are normally found in numbers in the submucous coat of the appendix. There is not any marked involuntary atrophy of the lymphoid tissue of the appendix in persons between the ages of 10 and 50. There seems to be a definite relationship between lymphoid hyperplasia of the appendix in children as well as adults and clinical symptoms of colicky pain in the lower part of the abdomen.

2. *Eosinophil Infiltration of the Appendix.*—Eosinophilia of the mucous membrane of the appendix is a normal phenomenon, at least in the tropics. Eosinophil infiltration of the submucosa of the appendix is evidence of chronic appendicitis.

AUTHOR'S SUMMARY.

THE MORBID ANATOMY OF SPRUE. F. P. MACKIE and N. H. FAIRLEY, Indian J. M. Research **16**:799, 1929.

The changes in the tongue are those which have already been described by other observers. The mucous membrane is thinned and atrophic and the lingual papillae may disappear. There is desquamation of the epithelial layers and occasionally loss of tissue amounts to superficial ulceration with little sign of inflammatory reaction. The changes in the intestine are most marked in the ileum, but are present to some degree throughout the whole tract. They are chiefly those of thinning and atrophy of the mucous membrane with marked degeneration and ultimately the almost complete disappearance of the absorptive and secretory epithelium. Here again, the change is one of degeneration and aplasia, and if it is preceded by inflammation there is little evidence of such in the terminal stages of the disease. There is evidence of blood destruction in the mucosa suggesting the absorption of some hemolytic substance from the intestine and the destruction of blood in situ. The disposition of micro-organisms in the gut wall favors the view that there is antemortem invasion by bacteria such as is known to occur in conditions of malnutrition due to vitamin deficiency. A specify atrophy of cardiac muscle out of all proportion to any decrease explicable in terms of mere starvation was noted in two cases of our series. On the other hand, the depreciation in the weights of the other viscera—notably that of the liver, spleen and kidneys—can be explained on the latter basis. The liver, kidney and the suprarenals sometimes show microscopic changes of a degenerative nature such as might be induced by the action of a toxin. Iron pigment is laid down in moderate amount, especially in the liver, but not in the same quantities as characterize pernicious anemia. The bone-marrow as seen in the femur or tibia shows in most cases marked aplasia. The red marrow, when present, is much reduced in quantity, though in two instances there was extensive hyperplasia similar to that seen in pernicious anemia. A moderate grade of hyperplasia was seen in another case. Such observations suggest that in sprue there is a toxin which primarily stimulates and later leads to the exhaustion of the hemopoietic function, so that in terminal stages of the diseases an almost complete aplasia results. This supposition is borne out by the condition of the blood as seen during life. These and other studies lead us to believe that sprue is primarily a disease of the intestinal tract which, if progressive, results ultimately in degeneration and destruction of the absorbing and secretory tissues and the production of a condition of slow progressive starvation. The absorption of toxins from the damaged mucosa perhaps associated with actual bacterial invasion, appears to be an important factor in the progressive anemia and other late manifestations of the disease.

AUTHORS' SUMMARY.

CULTURES OF BLOOD LEUKOCYTES: FROM LYMPHOCYTE AND MONOCYTE TO CONNECTIVE TISSUE. ALEXANDER MAXIMOW, Arch. f. exper. Zellforsch. **5**:169, 1928.

The lymphocytes and the monocytes of the mammalian blood in vitro are transformed in the course of a few hours into large, ameboid, phagocytic, dye-storing elements. These are identical in origin, structure and function with the

polyblasts or mononuclear exudate cells as found in inflamed tissue. Mitoses occur in the hypertrophying lymphocytes and monocytes, but are rare. In their transformation into polyblasts, the lymphocytes pass through a stage more or less similar to the monocyte. During the third to the fifth day of life in vitro, a large part of the polyblasts acquires a fibroblast-like aspect and structure. This condition is reversible. Under the influence of stimuli (strong light or, perhaps, heat) the cells rapidly contract, round off and again become ameboid. In later stages (from seven to twelve days), especially when cultivated in flasks, the fibroblast-like cells and many of the ameboid polyblasts are transformed irreversibly into typical fibroblasts. They lose the ability of motion, phagocytosis and storing of vital dyes. Their protoplasm develops tonofibrillae (fibroglia) which seem to arise through direct transformation of chondriosomes. These cells divide exuberantly by mitosis. First scattered singly at the periphery of the explant, they gradually assemble in groups and form strands and sheets. In still later stages (twelve to twenty-five to forty days) large cultures of connective tissue develop. They consist of fibroblasts and of resting polyblasts (histiocytes) scattered among the fibroblasts. The polyblasts gradually are transformed into fibroblasts in the same way as they do in the later stages of inflammation, in scar formation. The cultures thus obtained do not differ from connective tissue cultures of any other source. The histiocytic (polyblastic) and fibroblastic potencies of the lymphocytes of the blood are conclusively demonstrated. A large part of the lymphocytes of the blood of the chick in vitro turns into thrombocytes.

AUTHOR'S SUMMARY.

MAMMALIAN LYMPH IN TISSUE CULTURE: FROM LYMPHOCYTE TO FIBROBLAST. WILLIAM BLOOM, Arch. f. exper. Zellforsch. **5**:269, 1928.

The lymph of the thoracic duct of the rabbit contains few cells other than various sized lymphocytes. When such lymph is cultured in vitro, large and small lymphocytes change into typical inflammatory mononuclears or polyblasts which store lithium carmine. This transformation usually happens within from six to eight hours; it can be followed in the living cultures stained with neutral red and in the sections of fixed cultures. After the first ten or twelve hours many of the lymphocytes die but the polyblasts continue to develop. In a few days more the polyblasts become very large and change into typical fibroblasts. These experiments clearly indicate the importance of the lymphocytes as a source of the exudate mononuclear cells (polyblasts) of inflamed tissues.

AUTHOR'S SUMMARY.

THE ORIGIN AND NATURE OF THE MONOCYTE. WILLIAM BLOOM, Folia haemat. **37**:1, 1928.

An intense monocytosis is produced in rabbits either by infection with *B. monocytogenes* or by the intravenous injection of India ink, lithium carmine or saccharated iron oxide. In the latter experiments, the development of the monocytes into macrophages can be followed easily. The assumption found so frequently in the recent literature that monocytes arise directly from fixed cells — endothelium or reticulum endothelium — has not been demonstrated in any of the papers claiming this process. It was not demonstrable in my material. The monocytes develop by individual transformation of the lymphocytes in the blood stream, especially in the sinuses of the spleen and liver. In splenectomized rabbits, which were given injections of india ink into the portal vein and were then infected with *B. monocytogenes*, monocytes develop from hemocytoblasts in the bone marrow as well as from the lymphocytes in the lymph nodes. The monocytes should be sharply discriminated from free histiocytes, although they may develop into histiocytes in vivo and in vitro. Monoblasts do not exist. The so-called monoblasts of the literature are identical with lymphocytes when studied by any of the present hematologic and histologic methods.

AUTHOR'S SUMMARY.

THE CAUSE OF DEATH OF NEW-BORN CHILDREN. W. KLIMKE, Klin. Wchnschr. **8**:359, 1929.

In the Dortmund Institute the causes of death of new-born children from 1912 to 1914, inclusive, and from 1920 to 1928, inclusive (total 1,111), are: malformations, 6.2 per cent; birth traumas, 147 per cent; birth operations, 6.5 per cent; fetal complications (including diseases of all kinds), 20 per cent; maternal complications, 9.6 per cent; generalized atrophies, 22.2 per cent; unknown causes, 21.5 per cent. Congenital syphilis caused the death of 80. This as a cause diminished from 15.75 and 13.5 per cent in 1920 and 1922 to 0 per cent in 1928. Congenital pneumonia was observed in four stillborn and in eleven live-born infants. Aspiration pneumonia was found in nine new-born infants. Aspiration without reaction of the lungs caused the death of eighty-five stillborn and thirty-four live-born infants. Information regarding etiology was not obtained in six infants with generalized edema. Syphilis and nephritis were not present in the mother.

EDWIN F. HIRSCH.

SARCOMA OF THE VAS DEFERENS. W. KARO, München. med. Wchnschr. **76**: 374, 1929.

This is a brief account of a polymorph cell or spindle cell sarcoma of the right vas deferens. The tumor grew slowly over an interval of ten years.

EDWIN F. HIRSCH.

SPLENOMEGALY, A SYMPOSIUM. Verhandl. d. deutsch. path. Gesellsch. **23**:7, 1928.

W. Hueck, Leipzig, in discussing the anatomy of the spleen, in the first of twelve papers comprising the symposium, concluded that the blood courses through the spleen in a closed circuit at least in embryonic life. O. Lubarsch, Berlin, proposed the following grouping for splenic enlargements:

1. Splenomegaly in circulatory disorders.
   (*a*) Disorders in systemic circuit.
   (*b*) Disorders in portal circuit — thrombophlebitic splenomegaly.
2. Splenomegaly in blood diseases.
   (*a*) Leukemia.
   (*b*) Pernicious anemia.
   (*c*) Hemolytic jaundice.
   (*d*) Thrombopenic purpura.
   (*e*) Erythremia.
   (*f*) Splenogenous anemia.
3. Metabolic disturbances.
   (*a*) Sugar and fat.
   (*b*) Gaucher and Niemann-Pick.
4. Splenomegaly in combined circulatory and metabolic disturbances.
   (*a*) Cirrhosis of the liver.
   (*b*) Banti's disease.
5. Splenomegaly in infections and intoxications.
   (*a*) Acute.
   (*b*) Chronic as endocarditis lenta, tuberculosis, syphilis, malaria, kala-azar, etc.
6. Splenomegaly associated with tumors.
   (*a*) Primary.
   (*b*) Secondary.
7. Splenomegaly due to animal parasites.
   (*a*) Echinococcus.

B. Ugriumaw, Leningrad, summarized the observations in sixty cases of splenomegaly. Of forty-three recorded cases the spleen weight was as follows: in three cases, from 500 to 1,000 Gm.; in twenty-three cases, from 1,000 to 2,000 Gm., and in seventeen cases, over 2,000 Gm. The largest spleen weighed 6,500 Gm. Fifty-five specimens were obtained from males; the small number from females apparently being due to the reluctance of Mohammedan women to permit observation by a physician. Half of the specimens were obtained from the bodies of persons from 20 to 40 years of age. In fifteen cases the liver was of normal size; in fourteen it was small, and in thirty-one it was enlarged. The only lymph glands found enlarged were the mesenteric, periportal and retroperitoneal. Histologically, it was found impossible to differentiate Banti's disease from hemolytic jaundice. R. Rössle, Basel, discussed the condition of the spleen following hemorrhage; stressed the analogy between the edematous pulp in this condition and in such things as acute infections and maintained the presence of a splenic enzyme in both conditions. In the discussion following the presentation of the foregoing papers additional interesting features were observed. Bürger saw splenomegaly occur four times in infections with Bang's bacillus in the Kieler clinic in 1927. Ingestion of contaminated milk was the cause of the illness in all instances and the serum of the patients agglutinated Bang's bacillus and the bacillus causing Malta fever in high dilutions. Bang's bacillus was cultured in the blood. The characteristic picture of splenic enlargement developed after many weeks of remitting fever and the splenic tumor receded very slowly after treatment. Weicksel, in studying the red blood cells and the function of the spleen in blood transfusion, produced anemia in dogs and then used transfusion. He concluded that the spleen acted as a reservoir for the red blood cells. To further prove this he took photographs of the spleen in two projections and found that immediately after the transfusion the splenic volume was reduced one-fourth while in from one to two hours it enlarged to a size larger than before the transfusion. Helly maintained the normal vascular system of the spleen was closed but thought tears in the delicate splenic capillaries might aid in producing extravasations. He also held that because of the delicate construction of the spleen, injection methods are likely to produce erroneous pictures. Schilling stressed the three tissue components of the spleen, namely, the myeloid, lymphatic and reticulo-endothelial; he spoke of the spleen as a sponge the meshes of which might become engorged with any one of the aforementioned tissues, and advocated specifying which elements were involved in every type of splenic enlargement. Hamperl illustrated with a case report the impossibility of distinguishing the two types of lipoid cell splenohepatomegaly, Gaucher's disease and Niemann-Pick's disease. A child, 5½ months old, clinically had a lipemia, and splenic puncture brought out cells from 30 to 60 microns in diameter, round or oval with one or more peripheral nuclei and a homogeneous protoplasm staining blue with Mallory's connective tissue stain. In addition, these cells were found post mortem in the liver, spleen, lymph glands, bone-marrow, lymphoreticulum of the tonsils and thymus and in the mucosal stroma of the small bowel near Peyer's patches. The distribution of these cells was in accordance with the Niemann-Pick type. Furthermore, chemical analyses of the organs seemed to bear this out as the total lipoids were 9.6 per cent, total cholesterol 0.93 per cent and phosphorus 5.98 per cent. To confuse the issue, however, large quantities of Guacher substance were found. Abrikosoff cited instances of chronic splenomegaly in which fungi of the *Aspergillus* type were encountered morphologically and culturally. Sternberg doubted the occurrence of the fungi. He had seen encrustations of iron phosphate in a markedly atrophic spleen and noted the resemblance of these encrusted cords to fungi.

GEORGE RUKSTINAT.

CONCRETIONS OF THE CHOROID PLEXUS. FRANZ WINDHOLZ, Verhandl. d. deutsche path. Gesellsch. **23**:296, 1928.

Three different types of calcifications occur in the choroid plexus: (1) round, lamellated concretions, (2) sclerotic calcium incrustations of villi of the plexus and (3) angiogenic and amorphous petrifications of the supporting framework of

the plexus. The calcifications of the psammoma bodies are due to changes in the colloidal state of the protein substances caused by their increased lipoid content. The two last mentioned calcifications are of the dystrophic type in the presence of fat and fatlike substances. There is evidence of a marked fat and calcium metabolism of the plexus.

W. C. HUEPER.

THE CONDITIONS OF GROWTH IN TISSUE CULTURES. H. GUILLERY, Verhandl. d. Deutsche path. Gesellsch. **23**:301, 1928.

Tissue cultures of tissues of different proliferative activity grown in the same container show a gradual increase of the growth intensity of the more slowly growing cultures till it reaches that of the most rapidly growing culture. That this phenomenon is not caused by an exchange of growth substances between the cultures can be demonstrated by the separation of the individual cultures by glass plates, which do not interrupt the common plasma layer of the cultures. Glass plates placed between two cultures prevent this phenomenon. Metal mirrors placed at such an angle above a culture that rays emanating from the culture are reflected on another culture separated from the first one by a glass plate effect a reappearance of the phenomenon. The author concludes that radiating energy is responsible for the phenomenon in question.

W. C. HUEPER.

THE EFFECT OF VARIOUS EXOGENOUS FACTORS ON HOMOPLASTIC AND HETEROPLASTIC TRANSPLANTS. B. MORPURGE, Verhandl. d. deutsch. path. Gesellsch. **23**:330, 1928.

Skin grafts in rats of the same race are successful if the grafted animal is starved for several days and then insufficiently fed till the grafted tissue has become permanently attached. Grafts of guinea-pig skin on starved rats show a definite delay of necrosis. Similar results are obtained with animals fed with food heated to 150 C. for one hour and a half. Rats grafted with skin of animals of the same or different races and kept at temperatures ranging from plus 5 C. to minus 5 C. show similar good results.

W. C. HUEPER.

THE DISTRIBUTION OF VITAL STAINS IN THE BODY. L. LOEFFLER, Verhandl. d. Deutsche path. Gesellsch. **23**:336, 1928.

The author demonstrates in experiments with rabbits the dependency of the distribution of vital stains on the circulatory conditions in the different parts of the body. India ink injected into the vein of the ear is normally mainly retained in the spleen and liver. India ink injected with epinephrine is almost exclusively retained in the lungs. Similar differences are seen after injections into the mesenteric vein. Temporary ligation of the mesenteric artery preceding the injection of ink or simultaneous injection of histamine or chloroform produces similar results. Differences in the distribution of vital stains are seen if from 2 to 3 per cent solutions of trypan blue or lithiocarmine are used in conjunction with the aforementioned substances or procedures or after section of the ischiadic nerve. The dye particles are seen either in the cells or in clumps in the capillaries. Their location depends on the dispersity of the solution used and the colloidal status of the medium into which they are introduced. The particles of highly disperse solution enter the cells by diffusion, a purely physicochemical process, not by phagocytosis. The storage of granules of vital stains in the cells of the reticuloendothelial system of the spleen and liver represents only one of the many possibilities in the distribution of vital stains.

W. C. HUEPER.

THE PATHOGENESIS OF THE TUBERCULOSIS IN OLD AGE. H. E. ANDERS, Verhandl. d. Deutsche path. Gesellsch. **23**:406, 1928.

The tuberculosis in old age represents a late manifestation of the tuberculous primary lesion if the quiescent primary lesion of the chronic tuberculosis of the lung

is not taken into consideration. A reactivated tuberculosis of the lymph node (lymphoglandular endogenous reinfection of Ghon) was present in 35 per cent of the bodies examined. The spreading of the reactivated process may occur in an ascending or descending direction. The danger of hematogenous metastasis is present in the ascending type of spreading. Numerous isolated hematogenous organic tuberculous foci were observed in 69 per cent of the glandular tuberculosis and in 30 per cent of the organic tuberculosis. The organ systems arranged according to frequency of affection are the bony system, the urogenital system, the central nervous system and the suprarenals. The appearance of the endogenous, lymphoglandular reinfection at the forty-fifth year of life seems to support the conception that the tissue immunity of the lymphoglandular component of the tubercular primary lesion decreases or disappears at this age in a certain percentage of persons.

W. C. HUEPER.

INTERRENALISM AND INTERRENAL INTOXICATION. E. VON GIERKE, Verhandl. d. Deusche path. Gesellsch **23**:449, 1928.

Pseudohermaphroditismus masculinus externus with cortical adenomas in both suprarenal glands and female secondary sexual characteristics in a person 62 years old is considered as the result of the action of the interrenal system during fetal life. Hyperplasia of the cortex of the suprarenal glands occurs in infants during the first weeks of life suffering from digestive disturbances, intestinal diseases and toxic symptoms. The hyperplasia is either a nodular formation of lipoid cells or a diffuse hyperplasia of the cortex. Pseudohermaphroditism may be present or absent.

W. C. HUEPER.

DEVELOPMENT OF MACROPHAGES. M. SILBERBERG, Verhandl. d. Deutsche path. Gesellsch. **23**:456, 1928.

Silberberg concludes from his experiments with tissue cultures of chicken embryos and liver, spleen and vascular tissue of rabbit embryos with the addition of 5 per cent lithiocarmine solution that the histiocytes and monocytes are phylogenetically older than the lymphocytes and granulocytes. A transformation of macrophages into lymphocytes or granulocytes was never observed.

W. C. HUEPER.

THE PIGMENTED STRIAE OF THE VISCERAL PLEURA. F. ORSÓS, Verhandl. d. Deutsche path. Gesellsch. **23**:495, 1928.

The pigmented striae of the visceral pleura correspond in their location to the intercostal spaces. The primary cause of this local increase of pigment depends on the relatively lower tension of the pleural and subpleural tissue in the region of the intercostal spaces. The circulation of the lymph, blood and air is decreased in these areas. The striae are only distinct in the region of the upper lobes due to the concentrated tension of the diaphragm in the apical part and the minor respiratory movements of the upper lobes. Pigmented striae on the lower lobes are present in emphysema because the diaphragm is immobile.

W. C. HUEPER.

REACTION OF THE VESSEL WALL IN ARTERIOSCLEROSIS. M. SCHMIDTMANN and M. HÜTTICH, Virchows Arch. f. path. Anat. **267**:601, 1928.

Feeding rabbits with cholesterol led to differing results in the individual animals: In some the blood pressure rose, in others it remained the same. Cholesterol, and other colloidal substances, increased the sensitiveness of the animals to the pressor action of epinephrine. With preparations of excised arterial wall, it could be shown that the reaction of the tissue was of great importance in determining the sensitizing activity of cholesterol: The activity was marked in acid mediums, but entirely lost in alkaline mediums. It could also be shown that the ground

substance of young arteries is alkaline, while a progressive change toward the acid side takes place with age. Young growing rabbits did not respond to cholesterol feeding with increase in blood pressure, while in adult animals both increase in blood pressure and arteriosclerotic changes took place. According to these results, the cause for the difference in response to cholesterol between young and old animals appeared to be the physicochemical constitution of the vessel wall, especially the reaction of the ground substance. It is, of course, admitted that other factors enter into the predisposition of age for arteriosclerosis.

B. R. LOVETT.

DEVELOPMENT OF ATHEROSCLEROSIS. H. BEITZKE, Virchows Arch. f. path. Anat. **267**:625, 1928.

The author presents evidence, chiefly on a histologic basis, for the theory that local injury to the media is the primary event in the development of arteriosclerosis, and that the thickening and degenerative change of the intima is secondary to this. It is an exaggeration of the process which occurs physiologically in old age: As the media wears out, the intima becomes thickened. The finding of round patches of thickened intima, overlying weak points in the media, is evidence for this view. Calcification of muscle fibers in the media have been found from the twentieth year on, and over some of these places sclerotic patches develop. The most significant change, however, is tearing and degeneration of the elastic tissue, or, in muscular arteries, degeneration of the muscular fibers, so that the arterial wall bulges. These defects are compensated for by growth of the intima. One other type of early arteriosclerotic change, found only in the aorta, is cellular infiltration and scarring around the nutrient arteries, resembling syphilitic aortitis. There is a tendency for calcium and cholesterol to be deposited in the patches of thickened intima, but the author denies that this is the primary change. He attributes the fatty plaques in the aorta of young people to tearing of the intima during a sudden rise in blood pressure, and regards this lesion as entirely distinct from atherosclerosis.

B. R. LOVETT.

ANATOMIC CHANGES IN THE KIDNEYS OF INFANTS. L. SCHWARZ, Virchows Arch. f. path. Anat. **267**:654, 1928.

Histologic examination of the kidneys of infants revealed inflammatory and infiltrative changes regularly associated with pneumonias. These were similar to the changes described by Schridde and Councilmann in scarlet fever, and consisted of progressive stages: round cell collections in the capillaries, interstitial infiltration of lymphocytes or of plasma cells, and finally connective tissue scars. They occurred in infants dying in the fourth week of life or later, at which time pyuria also was most frequently observed. Inflammatory and infiltrative renal changes were rarely found under three weeks, and then were chiefly of lymphatic nature. They were frequently associated with disease in the mother. The glomerular changes described by Herxheimer were observed in 30 per cent of cases in the first three weeks, and in 100 per cent of infants over that age with inflammatory renal changes. Since in almost all instances adequate anatomic basis for the change was found, the view of Herxheimer that it is a congenital malformation could not be supported.

B. R. LOVETT.

LIPOID AND IRON DEPOSITION IN THE SUPRARENALS AND TESTES IN INFANCY. A. TOBECK, Virchows Arch. f. path. Anat. **267**:690, 1928.

The bodies of 100 infants under 1 year of age were examined for the lipoid and iron content of the suprarenals and testes. Lipoid was found chiefly in the cells of the inner zone of the suprarenal cortex, and the amount appeared to be markedly influenced by the presence of disease. Thus it was increased in acute inflammations, and reduced in chronic septic processes. Iron, present in the

reconstruction zone of the cortex from the fifth week on, increased until the fifth month and then decreased until the end of the year. Its presence was attributed to hyperemia and slight hemorrhages during growth of the cortex.

In the testes, lipoids were found constantly in the interstitial cells without relation to disease, but the presence of lipoid in the germ cells, found only occasionally, appeared to be pathologic. Iron was present in the interstitial cells from the eighth day on. No relationship could be demonstrated between the suprarenals and testes with regard to lipoid and iron metabolism.

B. R. LOVETT.

FORMATION OF TRUE STONES IN THE SMALL INTESTINE. H. BARTH, Virchows Arch. f. path. Anat. **267**:716, 1928.

True enteroliths, composed largely of inorganic material, are usually found only in the large intestine. In the case here described, eleven true stones were found at autopsy in a pouch of the ileum, which had apparently arisen following an operation for carcinoma of the sigmoid twenty years previously. The stones were facetted, and consisted of 80 per cent inorganic material, mostly calcium salts, around a core of feces.

B. R. LOVETT.

PEPTIC ULCER OF THE STOMACH AND DUODENUM IN THE DOG. K. HOSOMI, Virchows Arch. f. path. Anat. **267**:726, 1928.

In fifteen cases of plastic operation on the common bile duct in dogs, erosions of the stomach and duodenum were produced in seven, and in four ulcers of the duodenum with erosions and hemorrhages in the stomach. Since narrowing or occlusion of the duct was invariably present, the cause of the ulcers was thought to be in part the disturbance in flow of bile. Other factors suggested were adhesions of the duodenum, inflammation of the bile passages, postoperative infection and trauma. The author regards peptic ulcer as a local disease, and not as a manifestation of general disease.

B. R. LOVETT.

TABETIC ARTHROPATHY. A. R. MORITZ, Virchows Arch. f. path. Anat. **267**:746, 1928.

Moritz made an exhaustive histologic study of the knee joints of a woman dying with tabes and syphilitic aortitis. There was marked arthritis of both knees, with genu varum and subluxation on the left side, and genu valgum on the right. Macroscopically, the cartilage, where exposed to excessive strain, appeared white, rough and bulging from proliferative and degenerative changes. Where the pressure was least, the cartilage was normal or atrophic. The condyles of the femurs and tibias showed thickening of the spongiosa, with cartilaginous adhesions obliterating the intercondyloid fossae. Exostoses were numerous on the left side, but not on the right.

The chief microscopic changes in the cartilage were proliferation of the cells with increase in volume of the ground substance. More advanced changes consisted of mucoid degeneration of the ground substance, with farther growth of the cell columns, as in preparation for enchondral ossification. Signs of atrophy from disuse were evident in places relieved from pressure. Here the cartilage was surrounded by a fibrous covering, and was itself partly fibrocartilage. Enchondral ossification, following the proliferative changes and altering the shape of the joint, played a prominent rôle in the arthritic process. Cartilage-covered exostoses were found arising not only from the cartilaginous joint surfaces but also from the periosteal surfaces. Evidence of wear and tear on the joint surfaces was a prominent feature, with necrosis of the fibrous or cartilaginous coverings, and replacement by a dark red fibrinous substance. Results of trauma were also seen: tears followed by callus formation. Intra-articular fracture, an important occurrence in the tabetic joint, was probably responsible for marked shortening of the lateral condyle of one femur. New bone formation had taken place at the

insertions of the ligaments, and especially over the condyles of the tibiae. Here the process had given rise to new joint surfaces, shaped to meet the functional demands. Study of a second case in a less advanced state revealed that this new bone was probably periosteal callus, due to loosening of the intact periosteum from the bone. Pieces of old cartilage embedded in the new bone indicated that slight breaks had occurred previously.

B. R. LOVETT.

INVOLUTION AND REGENERATION OF THE THYMUS UNDER THE INFLUENCE OF BENZENE. J. E. LEWIN, Virchows Arch. f. path. Anat. **268**:1, 1928.

The ingestion of benzene leads to atrophy of the thymus in the rabbit, the picture of "accidental involution." There are two stages: the formation of an inverted gland and the period of connective tissue development with atrophy of lobules. The first period is characterized by a rapid lymphocytic disintegration and activity of the reticulo-endothelial cells. The latter cells hypertrophy, become isolated and form free macrophages, hemocytoblasts which in turn develop into pseudo-eosinophils, premyelocytes and myelocytes. In the second period besides an overgrowth of interlobular connective tissue there is formed a close-meshed network of collagen bundles within the lobules. The reticular cells play a prominent rôle in the formation of new lymphocytes, a lesser rôle by the adventitial cells. The regeneration of the thymus is accompanied temporarily by myelo- and erythropoiesis, most pronounced in the cortex.

V. C. JACOBSEN.

COMPLETE NECROSIS OF THE WANDERING SPLEEN WITH COMPENSATORY PERIPHERAL NODULAR HYPERPLASIA OF SPLENIC TISSUE. J. CATSARAS, Virchows Arch. f. path. Anat. **268**:181, 1928.

Obstruction of the main splenic artery of the misplaced spleen is the cause of necrosis of the greater portion of the organ, while the peripheral parts receiving their blood supply from the capsule remain alive. These living fragments are supported by a more or less favored collateral circulation and undergo a consequent hypertrophy, producing a striking multinodular distortion of the organ.

V. C. JACOBSEN.

HISTOLOGIC CHANGES IN ENDOCARDITIS LENTA. T. ISTAMANOWA, Virchows Arch. f. path. Anat. **268**:224, 1928.

Thirty cases of endocarditis lenta, in which the histologic changes were not very specific, were studied. There were two main types: a rapid, acute form with toxins affecting liver and a lymphocytotoxin acting on spleen and lymph nodes. The tendency to embolism accounts for most of the fatalities in this group. The frequent focal nephritis is due to bacterial emboli. There is a sharp reaction of the reticulo-endothelial apparatus which, however, does not involve the whole vascular system. A second type more chronic and milder, is without gross visceral changes. There is progressive weakness of the heart and hyperemia of the internal organs, hyperplasia of the reticulo-endothelial cells such as occurs in many other infections, with a transformation of lymphocytes into plasma cells.

V. C. JACOBSEN.

BONE SARCOMA ARISING IN A CASE OF OSTITIS DEFORMANS (PAGET). A. VON ALBERTINI, Virchows Arch. f. path. Anat. **268**:259, 1928.

The case of a woman, aged 51, who had had typical Paget's disease for at least five years is reported. The pelvic girdle, left femur and tibia were most affected. Spontaneous fracture occurred and revealed a sarcoma arising in the fibrous marrow with tendency to osteogenic type in femur and tibia. The tumor in the shaft was of polymorphocellular type. At death, metastases were found in the lungs, liver and kidneys, and tumor thrombus in the left iliac vein. The ques-

tion of traumatic etiology was discussed, but the author believes great care should be used in assigning importance to trauma.

V. C. JACOBSEN.

BILATERAL CHROMAFFIN TUMORS OF SUPRARENALS WITH HYPERTENSION. KURT SCHRÖDER, Virchows Arch. f. path. Anat. **268**:291, 1928.

A woman, aged 42, with hypertension and diabetes, at autopsy showed bilateral chromaffin suprarenal tumors, hypertrophy of the heart, atherosclerosis of the large and medium vessels and atrophy of the pancreas. The hypertension, vessel changes and hypertrophy of heart were regarded as due to excessive suprarenal secretion by the tumors, because of the strongly positive Vulpian iron chloride reaction of the tumors. The vessel changes were those of ordinary atherosclerosis.

V. C. JACOBSEN.

THE MORPHOLOGY OF EXPERIMENTAL HYPERTHYROIDISM PRODUCED BY SYSTEMIC FEEDING WITH THYROID SUBSTANCE. E. KLIWANSKAJA-KROLL, Virchows Arch. f. path. Anat. **268**:374, 1928.

Feeding young rats with thyroid substance in the first ten to twenty days produces slight adrenal changes. In thirty days there is a hypertrophy of adrenal cortex. The longer the feeding period, the more prominent the increase in size of the adrenal glands. The change is confined largely to the cortex, and is due to an increase in fatty material within the cells. This accumulation of fat in the cortex is the result of an infiltration from the blood which showed a hyperlipemia.

V. C. JACOBSEN.

A RARE FORM OF FULMINATING GLOMERULO-NEPHRITIS. R. HÜCKEL, Virchows Arch. f. path. Anat. **268**:395, 1928.

A report is given of a case of acute nephritis in a woman, aged 53, which was fatal in two and one-half days. The histologic picture is of a toxic focal glomerulo-nephritis due to hemolytic streptococcus infection. The focal lesions present are regarded as not embolic. The toxin attacks the first part of the glomerular capillary at the dilated end of the afferent artery, with thrombus formation and destruction of endothelium, and to some extent the walls of the afferent arteries. In some respects, it resembles a diffuse nephritis. Mixed types occur, but greatest importance is given to the factor producing the focal lesion.

V. C. JACOBSEN.

THE RÔLE PLAYED BY THE LUNG, LIVER AND SPLEEN IN FAT AND LIPOID METABOLISM. G. L. DERMAN and SAMUEL LEITES, Virchows Arch. f. path. Anat. **268**:440, 1929.

Following the ingestion and intravenous injection of oleic acid into dogs, the fatty acid mixed with neutral fat and lipoid can be demonstrated in the lungs, liver and spleen. Oral administration of olive oil led to its deposit in the alveolar epithelium of the lung, liver cells, Kupffer cells and the reticulo-endothelium of the spleen. Split products are also present in liver and spleen, while after lienectomy or ligation of the splenic vessels split products can still be demonstrated in the lung. Following ingestion of a solution of cholesterol in olive oil by mouth, cholesterol and its esters can be found in the lung, liver and spleen. Intravenous injection of this cholesterol solution is not followed by its accumulation in the lung and liver; only a mixture of neutral fat and fatty acids can be observed. Oral and intravenous feeding of lecithin results in no accumulation of lecithin in the lungs, liver or spleen. Histochemically, only neutral fat and fatty acids can be shown. The authors conclude that the lungs, liver and spleen play an active rôle in fat and lipoid metabolism, and that the metabolites may be built up into other fats and lipoids. There is an endogenous as well as exogenous fat and lipoid infiltration of the organs.

V. C. JACOBSEN.

THE PATHOLOGIC ANATOMY OF PLUMBISM. HELEN FREIFELD, Virchows Arch. f. path. Anat. **268**:456, 1928.

The changes in the meninges are slight, the greatest damage being in the brain substance where there are many foci of phagocytic cells about nerve cells and fibers. There is proliferation of the endothelium of the capillaries. The earliest change noted is a metachromasia of Nissl's granules. Possibly an alkalinization of the tissues occurs. In the cerebellum are changes in the Purkinje cells as well as in the vessels. Gliosis is present in the anterior horns of the spinal cord which is postulated as being due to alterations of metabolism of the sympathetic nervous system, the products of metabolism accumulating in the perineural and endoneural cells leading to connective tissue proliferation. Nerve fibers are irritated to cause colic. There is formation of Renautis bodies by connective tissue overgrowth in the nerve sheaths, and analogous changes occur in the ganglion cells of the ganglion solare. In the spinal nerve roots, Gombalt's periaxial neuritis and proliferation of Schwann's cells are found. The arteries of the spinal cord and the kidney show Heubner's type of intimal proliferation. Innervational disturbances of the vessels cause the vascular changes. In the bone-marrow there is a proliferation and then a flood of megakaryocytes into the circulation of the obstructing lung capillaries. The anemia is hemolytic, but only small amounts of iron are deposited in the spleen and the bone-marrow and none in the liver. Hyperplasia of the reticulo-endothelial cells in the internal lymph nodes is caused by lead albuminate passing from the intestine to the nodes.

V. C. JACOBSEN.

MALFORMATIONS OF EXTRAHEPATIC BILE DUCTS. FRIEDRICH FEYRTER, Virchows Arch. f. path. Anat. **271**:20, 1929.

The author reviews and groups the reports available in the literature; he adds three original observations. Cystic dilatation and atresia may be found together; the malformations are generally multiple. The teratologic termination point is early. The causes are unknown.

ALFRED PLAUT.

A PECULIAR FORM OF SYSTEMIC BONE-MARROW DISEASE COMBINED WITH OSTEOSCLEROSIS. A. A. WASSILJIFF, Virchows Arch. f. path. Anat. **271**: 134, 1929.

A man, aged 30, had pain in the legs for five years, severe anemia and thrombopenia. At autopsy, diffuse osteosclerosis, pachymenginitis hemorrhagica interna and subserous hemorrhages were found. The bone-marrow, which was gray and pink, was full of bone lamellae. Most of it was supplanted by large honey-combed cells with one small nucleus; they were from ten to fifteen times larger than a lymphocyte. The blood vessels in the periosteum and in the bone marrow contained heaps of such cells; similar cells were found in the lymph nodes and lungs. The reticulum and endothelium in the lymph nodes were hyperplastic. The ground substance of the protoplasm of the large cells took no stain. This disease cannot be classified with any known systemic disease; it obviously is no tumor.

ALFRED PLAUT.

ANATOMY OF GAUCHER'S DISEASE IN INFANTS. H. HAMPERL, Virchows Arch. f. path. Anat. **271**:147, 1929.

In addition to the usual localizations (spleen, liver, lymph nodes and bone-marrow), Gaucher cells were found in the cortex of the thymus, tonsils, adenoids, lymph follicles of the intestine, zona reticularis of the suprarenal gland, and perhaps the lung. Kerasin and cerebrosin constituted 3 per cent of the dry substance of the spleen. The lipoids, phosphorus and total cholesterol were high, similar to the figures in Niemann-Pick's disease. The presence of Gaucher cells in the other organs is due to the special behavior of connective tissue and reticulum in the first year of life.

ALFRED PLAUT.

BAMBERGER-MARIE'S DISEASE. T. KONSCHEGG, Virchows Arch. f. path. Anat. **271**:164, 1929.

The histologic description is given of bone lesions in a man, aged 56, who had typical hypertrophic secondary pulmonary osteo-arthropathy. Sarcoma of vertebrae was the underlying disease.

ALFRED PLAUT.

THE MORPHOLOGIC CHANGES IN BLOOD AND HEMATOPOIETIC ORGANS UNDER THE INFLUENCE OF BENZENE AND ITS DERIVATIVES. A. WORONOW, Virchows Arch. f. path. Anat. **271**:173, 1929.

Rabbits withstood subcutaneous injections of xylene for several weeks, and after initial leukopenia, had leukocytosis up to 30,000. Since xylene is as good a fat solvent as benzene, one cannot explain the action of benzene by its fat-solving power. Phenol, even in high doses, proved innocuous. Considering the CH_3 groups of xylene important, the author injected other methylated phenols like toluol, cumol and cymol, with one and three CH_3 groups, respectively. They acted like xylene. Some of the pathologic forms of leukocytes were similar to those found in myelogenous leukemia. The author hopes that in varying such experiments one may succeed in producing myelogenous leukemia.

ALFRED PLAUT.

SPLEEN LESIONS IN MALARIA. B. A. PHOTOTAKIS, Virchows Arch. f. path. Anat. **271**:194, 1929.

In hyperacute malaria with death during the first attack, the enlarged spleen is chocolate-colored, grayish black or deep black; it is pulpy and may flow in the pan. Such colors of spleen are not found in any other infectious disease; they are characteristic of malaria, in the peracute form. In such spleens the reticulum shows no reaction; there is only hyperplasia of the endothelium. In acute malaria, the reticulum reacts; in chronic malaria, the connective tissue does also.

ALFRED PLAUT.

PARTICIPATION OF BOWMAN'S CAPSULE IN DIFFUSE GLOMERULONEPHRITIS. EDMUND RANDERATH, Virchows Arch. f. path. Anat. **271**:197, 1929.

A network of fine capillaries surrounds the glomerulus; it is connected with the intertubular capillaries. Accumulations of leukocytes in such periglomerular capillaries are found together with circumscribed swelling of the adjoining parietal layer of the capsule; over this swelling the lining cells desquamate. Although micro-organisms, pneumococci, for instance, were found in capillaries nearby (autopsy immediately after death), the lesions are not to be explained as directly due to bacterial influence. The mesenchyme of the capsule must have become permeable, and that leads to the changes in the glomerular epithelium. Spindle-shaped oxydasepositive cells were found in the Bowman's capsule. The hyaline thickenings of the capsule in older cases may be later stages of the described lesion. Randerath considers the term "glomerular epithelium" misleading; he speaks about "glomerulothel" in analogy to Maximow's mesothel.

ALFRED PLAUT.

LYMPHOGRANULOMATOSIS, PARTICULARLY ITS PULMONARY FORM. A. BERNSTEIN, Ztschr. f. Tuberk. **52**:202, 1928.

A case of lymphogranulomatosis with exclusive localization in the lungs is reported with detailed clinical and necropsy data.

MAX PINNER.

CARCINOID OF THE SMALL INTESTINE AND APPENDIX. BJARNE DAHL, Norsk Mag. f. Laegevidensk. **90**:233, 1929.

Three cases are described: In one the tumor was benign and of extremely slow growth; in the other two cases large glandular metastases gave rise to

mechanical disturbances, but here also the microscopic sections showed a benign nature of the growth with regular cells, no mitoses and no inflammatory reaction in the surrounding tissues. The relatively benign nature of carcinoid and its metastases is emphasized.

EXPERIMENTAL INVESTIGATIONS OF HEMATOGENOUS STAPHYLOCOCCAL NEPHRITIS. MARTTI HÄMÄLÄIEN, Arb. a. d. path. Inst. d. Univ. Helsingfors **5**:271, 1929.

Human hematogenous staphylococcal nephritis occurs in two main morphologic forms, which pathogenetically also represent two groups: mycotic eliminative nephritis and emboli suppuration nephritis. These two types were reproduced experimentally in rabbits. Leaving out of consideration typical embolic staphylococcal nephritis, the author includes the other kind in the same pathogenetic group as due to capillary metastasis. This group takes in all cases due to elimination of staphylococci and also those of the embolic-suppuration type in which many foci develop in the kidney, especially in the cortex. Mixed forms may occur.

PHIL SHAPIRO.

THE GENESIS OF ACUTE VALVULAR ENDOCARDITIS. OSTEN HOLSTI, Arb. a. d. path. Inst. d. Univ. Helsingsfors **5**:401, 1928.

The frequent discrepancy between obvious clinical signs and negligibly slight gross postmortem observations led the author to investigate histologically the entire leaflets in cases of valvular heart disease. He took complete sections from all four valves and their roots. He found that inflammatory changes were much more frequent than one would suspect from gross examination. In twenty-eight cases of ulcerous, verrucous and syphiltic endocarditis there was a valvulitis in 66, or 59 per cent, of the 112 valves. In a control group of 64 cases there were changes in 49, or 19 per cent, of the 256 valves, and these were only slight. The right valves were more frequently affected than the left, and the auriculoventricular more than the semilunars. Rarely is the valvulitis only superficial (12 per cent). A localized defect in the endothelium is followed by a reactive process in the subendothelium. The valvulitis is often only deep (41 per cent) and the gross changes so slight that without histologic examination they would go undetected. Vascularization begins at the rot of the valve, is preceded by exudation and is followed by fibroblastic proliferation. It proceeds toward the periphery. This is more common in the right side of the heart than in the left. Combined deep and superficial valvulitis is most common. It may represent two independent processes, with or without fusion; a deep valvulitis may extend to the endothelium, or a superficial valvulitis may burrow backward to the root of the valve. The deep lesions, detectable often only by microscopic examination, may clarify the incongruities that arise between clinical murmurs and inadequate gross observations at autopsy.

PHIL SHAPIRO.

NORMAL AND MORBID HISTOLOGY OF THE VESSELS IN THE MUCOSA OF THE NOSE AND MAXILLARY ANTRUM WITH SPECIAL REFERENCE TO ATROPHIC RHINITIS. ARNO SAXÉN, Arb. a. d. path. Inst. d. Univ. Helsingsfors **5**:733, 1928.

Fundamentally, the atrophy in ozena is not nutritive. Circulatory disturbances are not the primary cause of the atrophy but they may act as secondary factors. The changes in the vessels involve especially the veins and capillaries in the erectile tissue, while the arterial changes are of less importance.

PHIL SHAPIRO.

Microbiology and Parasitology

THE BACTERIOLOGY OF MASTOIDITIS IN INFANTS. MARY B. SPAHR, Am. J. Dis. Child. **37**:541, 1929.

Cultures from the middle ear of an infant are valueless as indications of the causative organism in an accompanying mastoiditis. Infants suffering from otitis

media and showing the constitutional symptoms of vomiting, diarrhea and failure to gain in weight often have infected mastoid antrums. In all cases in which intestinal organisms (*B. coli-communior* or bacillus or Morgan) were found on culture from the mastoids, the prominent clinical symptom was diarrhea, accompanied in some instances by vomiting. Pneumococci, streptococci and staphylococci were also frequently found in cultures from the mastoids of infants. These organisms did not give rise to a characteristic symptomatology.

AUTHOR'S SUMMARY.

THE RELATION OF THE TONSILS TO ACUTE RHEUMATISM DURING CHILDHOOD. ALBERT D. KAISER, Am. J. Dis. Child. **37**:559, 1929.

An analysis of 439 cases of rheumatism in children discloses the following facts: The most susceptible age for the first attack of rheumatism was between 8 and 14 years. Nearly twice as many first attacks of rheumatism developed in children whose tonsils were still present. Recurrent attacks occurred 10 per cent less often in children who had had their tonsils removed after the first attack than in those whose tonsils had not been removed. The incidence of carditis as a complication in acute rheumatism was nearly as frequent in children who had undergone a tonsillectomy as in those who had not. Chorea occurred as a complication in acute rheumatism with equal frequency in children operated on and not operated on, but the association of carditis with chorea was less frequent in children whose tonsils had been removed. Tonsils are the avenue of infection in many cases of rheumatism and bear a definite relationship to this disease. Their removal should be advocated for the rheumatic and the potentially rheumatic child, until more is known of the etiology of rheumatism.

AUTHOR'S SUMMARY.

EXPERIMENTAL WHOOPING COUGH. LOUIS W. SAUER and LEONORA HAMBRECHT, Am. J. Dis. Child. **37**:732, 1929.

The injection of *B. pertussis* (Bordet-Gengou) into the larynx of five healthy young monkeys was followed, after a period of incubation of from one to three weeks, by spontaneous, paroxysmal coughs. Similar coughs followed inoculation in the nares of three healthy young monkeys. The total and differential white cell counts usually showed the transient lymphocytosis characteristic of pertussis in human beings. The bacillus was recovered from deep throat cultures; also from the larynx, trachea and lungs after death. The bacillus was recovered during the height of the cough from an animal that had been inoculated with the bacillus recovered, in turn, from the lung of another coughing animal. Animals that recovered were immune to subsequent injections of various strains of *B. pertussis*.

AUTHORS' SUMMARY.

PSEUDOMEMBRANOUS ENTEROCOLITIS AND MASTOIDITIS ASSOCIATED WITH AN INFECTION WITH MORGAN'S BACILLUS. T. LEONARD SUTTON, Am. J. Dis. Child. **37**:814, 1929.

A case of pseudomembranous enterocolitis is presented in which the clinical evidences of infection of the middle ear developed later, and in which Morgan's bacillus was isolated from the heart blood and from the middle ear.

AUTHOR'S SUMMARY.

STUDIES ON FILTRABLE VIRUSES (VACCINE VIRUS). ROBERT N. NYE and FREDERIC PARKER, JR., Am. J. Path. **5**:147, 1929.

Further experiments are described demonstrating the multiplication of vaccine virus in tissue cultures. Vaccine virus could not be cultivated using killed tissues or under anaerobic conditions. The virus when suspended in Locke's solution, was destroyed if heated to 55 C. for twenty minutes or to 37.5 C. for twenty-four hours. The optimum hydrogen ion concentration for survival of the virus in

glycerin was found to be p_H 7. After centrifugalization, the bottom layer contained more virus than the top layer. The virus could not be filtered through a Mandler filter. Experiments on the viricidal action of hyperimmune calf serum are described.

AUTHORS' SUMMARY.

THE OCCURRENCE OF TUBERCULOID REACTION IN THE INGUINAL GLANDS IN EARLY SYPHILIS. H. E. MICHELSON, Arch. Dermat. & Syph. **19**:66, 1929.

The histologic character of the inguinal nodes in early syphilis is variable, two distinct lesions being observed. One is a subacute proliferative and exudative inflammation, which may be termed nonspecific lymphadenitis; the other is a tuberculoid reaction which histologically is indistinguishable from that found in tuberculous adenitis. The inguinal nodes from twenty-nine persons with early untreated syphilis were excised and examined microscopically. Nonspecific inflammation occurred in twenty-one and tuberculoid reactions in eight. Tuberculoid structures were found much earlier in the inguinal nodes than in cutaneous lesions. If the tuberculoid reaction is a manifestation of high resistance, then probably the production of immunity or antibodies begins early in the lymphatic system.

AUTHOR'S SUMMARY.

BACTERIA IN THE TONSILS. L. M. ROLVOGT and S. J. CROWE, J. A. M. A. **92**:962, 1929.

The tonsils and adenoids were removed at operation in 100 patients with a history of acute attacks of tonsillitis. After washing in 70 per cent alcohol, the tonsils were ground in sand and cultures were made. The hemolytic streptococcus was the predominating organism grown in 91 per cent and the staphylococcus in 8 per cent. In one case no growth was obtained. There is no apparent connection between the predominating type of organism found in the tonsils and the clinical symptoms. The majority of these cultures were made during the winter months, and all were made between November, 1927, and April, 1928. More than 50 per cent of the patients from whose tonsils a hemolytic streptococcus was grown in pure culture were children under 11 years of age. The majority of those in whom a staphylococcus was the predominating organism were over 25 years of age. The average time between the last acute attack of tonsillitis and the tonsillectomy was one month. In eighty-one cases the hemolytic streptococcus was the predominating organism in both the tonsils and the adenoids. In eight there was a heavy growth of staphylococcus from both the tonsils and the adenoids. In ten there was a heavy growth of staphylococcus from the adenoid culture and a pure culture of streptococcus from the tonsils. A culture made by swabbing the surface of the tonsil is a reliable index of the predominating organism in the crypts.

AUTHORS' SUMMARY.

INFESTATION WITH DIPHYLLOBOTHRIUM LATUM, FISH TAPEWORM, WITH ESPECIAL REFERENCE TO NATIVE CASES. MOSES BARRON, J. A. M. A. **92**:1587, 1929.

Native infestation with the fish tapeworm is rapidly increasing in the United States and Canada. There appear to be three endemic areas established thus far: the lakes of the northern peninsula of Michigan, the lakes in the northern part of Minnesota and the lakes around Winnipeg in Canada. The complete life cycle of the parasite has been carefully worked out in America, as well as in Europe. Two intermediate hosts and one definitive host are the means through which the life cycle is completed. Infestation in man can occur only through the ingestion of raw or insufficiently cooked fish. A large proportion of the population of Finland is infested because of the consumption of raw fish. Of the cases of native infestation, the larger percentage occur in Jewish women and children who have tasted the raw minced fish in the preparation of gefüllte

fish. Infestation of fish occurs not only through their ingestion of infested crustaceans but also through the ingestion of other fish that are infested. Pernicious anemia does not occur any more often through infestation with the fish tapeworm than through infestation with the beef tapeworm and the incidence is slight. The removal of the tapeworm apparently does not alter the course of the anemia, nor does the presence of the tapeworm modify the profoundly beneficial effect of the feeding of liver in bringing back the blood picture practically to normal. Thus far, nineteen authentic cases of native infestation have been reported, three of which were added here. Undoubtedly, there could be included many other cases of patients who, though not born in America, obviously were infested after coming to this country.

AUTHOR'S SUMMARY.

TULAREMIA IN MINNESOTA. E. C. HANSON and R. G. GREEN, J. A. M. A. **92**:1920, 1929.

Cases of tularemia in Minnesota are reported. In one case the infection followed the bite of a wood tick (*Dermacento variabilis*), and in another it followed the bite of a finger by a cat.

CHRONIC MENINGOCOCCEMIA. W. R. GRAVES, A. D. DULANEY and I. D. MICHELSON, J. A. M. A. **92**:1923, 1929.

A case of chronic meningococcemia is described. Meningococcus infection is classified as (1) acute meningococcemia, fulminating or followed by meningitis and (2) subacute or chronic meningococcemia, with or without metastasis. A table of thirteen cases of prolonged meningococcemia reported in this country is included.

DISSOCIATION OF B. ANTHRACIS. W. J. NUNGESTER, J. Infect. Dis. **44**:73, 1929.

A laboratory stock culture of *B. anthracis* aged under various culture conditions yielded six additional culture types. These forms have all been reisolated from the usual anthrax colony type, "purified" by over 100 serial single colony isolations. After similar purification all variants were caused to revert to the usual colony type. The form giving rise to the usual rough, gray colony has been designated as the R form. One variant formed small smooth raised colonies which were termed the S form. All forms were studied according to colony characteristics, morphology, variations in different mediums, and dissociation under different conditions in cultures and in vivo. The virulence was tested in mice and guinea-pigs; all variants when first isolated from the R form could produce death. R forms derived from avirulent forms were not virulent. R forms derived from slightly virulent forms had an increased virulence approximating that of the original R form.

FROM AUTHOR'S SUMMARY.

THE ACTION OF BACTERIA ON FAT. ROY H. TURNER, J. Infect. Dis. **44**:126 and 134, 1929.

1. Five groups of differential plating mediums for lipase-producing bacteria have been compared for sharpness of differentiation, sensitivity, inhibition of bacterial growth, and tendency to give false positive reactions.

Those mediums which depended on gross disintegration of tallow or globules of cottonseed oil emulsion for differentiation were found to lack sharpness of differentiation, to be low in sensitivity, but did not inhibit growth of organisms studied and gave no false positive reactions. The development of clear zones may be greatly facilitated by using fats made up of short chain fatty acids or by adding bile to the medium.

Those mediums which depend on hydrogen ion indicators for differentiation were found lacking in sensitivity due probably to the little effect which the higher fatty acids have on p_H, and they gave false positive reactions in the presence of fermentable carbohydrates.

The nile blue sulphate medium gave remarkable sharpness of differentiation and high degree of sensitivity, but inhibited the growth of certain organisms. The meaning and mechanism of fading zones is discussed; they do not seem to indicate the formation of lipase. Whether nile blue sulphate acts as a differential stain or as an indicator is discussed.

2. The action of a strain of lipolytic bacteria on the globules of an emulsion of cottonseed oil in a thin layer of agar medium containing nile blue sulphate has been observed with the microscope and photomicrographs made. To aid in explaining the observations on cottonseed oil, a similar study has been made of pure fats and combinations of two or more. What has been seen to happen to cottonseed oil is set forth with interpretations as follows:

A globule of oil, well removed from a bacterial colony, becomes blue, due to the staining of unsaturated fatty acids, oleic and linoleic, split by diffusible lipase. Part of the fatty acids are converted into soaps. There is diffusion into the agar surrounding the globule of blue staining material, probably mixtures of these same fatty acids and their soluble soaps. If near the colony, this material quickly becomes decolorized and disappears; if further away, this happens slowly. Marked shrinkage of the globule occurs; it usually takes a crescentic shape. This shape seems to be the result of surface activity of the remaining lipoid material, which no longer completely fills the cavity in the agar. Shrinkage of some globules is accompanied by protrusion of a bundle of crystals. These are crystals of the solid fatty acids, linoleic and palmitic, or their derivatives. Crystals are seen to form in the agar well removed from visible globules of oil. It is suggested that these are derived from lipoid material which existed in solution or colloidal suspension.

The method of study is of greatest value when used in conjunction with accurate quantitative methods.

AUTHOR'S SUMMARY.

A COMPARISON OF SEVEN STRAINS OF ORGANISMS CAUSING HUMAN BLASTOMYCOSIS. DOROTHY SPRING, J. Infect. Dis. **44**:169, 1929.

Different strains of organisms causing human blastomycosis, even within the Gilchrist group, differ materially; morphologically in test tube and hanging-drop cultures; in fermentation of sugars and resistance to certain dyes, and in virulence. Yeast cells in pus are sensitive to dyes to the same extent as those in culture. They resist heat at 48 C. for twenty minutes; so it appears that heat therapy does not promise success. Similarly, dye therapy does not rest on a scientific basis. Generalization of infection in laboratory animals occurs rarely except in mice. The mouse is the animal of choice for diagnostic tests, and it is difficult for the organism to gain a foothold at all in rabbits and to a less extent in guinea-pigs.

AUTHOR'S SUMMARY.

TABARDILLO, AN AMERICAN VARIETY OF TYPHUS. H. MOOSER, J. Infect. Dis. **44**:186, 1929.

Tabardillo is a distinct variety of typhus fever which can be differentiated from European typhus by inoculation in guinea-pigs. The disease observed in the southern United States is identical with tabardillo of Mexico and is distinct from Brill's disease observed in New York which belongs to the European variety.

AUTHOR'S SUMMARY.

SPONTANEOUS TUBERCULOSIS IN SNAKES. JOSEPH D. ARONSON, J. Infect. Dis. **44**:215, 1929.

Tubercles were found in the various organs of four garter snakes (*Thamnophis sirtalis)* found dead in the Philadelphia Zoological Garden. Large numbers of acidfast but not alcoholfast bacilli were observed within them. The tubercles consisted of a central area of necrosis surrounded by cells with a large, clear, vesicular nucleus, by connective tissue, and by some deeply staining smaller cells,

with numerous eosinophils scattered throughout. From the lesions was isolated an acidfast but not alcoholfast chromogenic bacillus that grows best from 20 to 25 C. and is pathogenic for garter snakes, frogs, goldfish, chameleons and red lizards, but not for guinea-pigs, rabbits, chickens or pigeons. The bacillus differs in cultural and antigenic character and in staining reaction from previously described pathogenic poikilothermic acidfast bacilli. The name *Mycobacterium thamnopheos* is suggested for this organism.

AUTHOR'S SUMMARY.

TWO OUTBREAKS OF FOOD POISONING PROBABLY DUE TO B. CLOACAE. ENOS B. BUCHANAN and EMERSON MEGRAIL, J. Infect. Dis. **44**:235, 1929.

An organism of the cloacae type was present, and organisms of the paratyphoid group were absent, in two outbreaks of food poisoning. The cultures of this organism obtained from the food produced a substance toxic for rabbits. From the epidemiologic and experimental data reported, it is probable that *B. cloacae* was the cause of these outbreaks.

AUTHORS' SUMMARY.

EPIZOOTIC LYMPHADENITIS IN GUINEA-PIGS. EMERSON MEGRAIL and ROBERT N. HOYT, J. Infect. Dis. **44**:243, 1929.

A small outbreak of epizootic lymphadenitis in guinea-pigs was shown to be due to β and γ types of streptococcus. *Staphylococcus albus* was also present, probably as a secondary invader. The source of the infection could not be ascertained. Experimental production of the disease was apparently through the skin.

AUTHORS' SUMMARY.

PRODUCTION OF COLDS WITH MICROCOCCUS CATARRHALIS. JOHN E. WALKER, J. Infect. Dis. **44**:254, 1929.

Two of three intranasal inoculations with *M. catarrhalis* in the same person were followed by typical colds. The inoculated organism was recovered on culture. In one instance the inoculated organism was not found on early culture, but was present later when the exudate became more mucoid. The experiments, taken in conjunction with two previous acute infections of the upper respiratory tract associated with *B. influenzae* and *B. bronchisepticus*, are believed to indicate that the bacteria cultivated from the nasal exudate are the primary cause of colds.

AUTHOR'S SUMMARY.

THE MORPHOLOGY OF COCCIDIOIDES IMMITIS. FLORENCE E. AHLFELDT, J. Infect. Dis. **44**:277, 1929.

A short historical sketch of the life cycle of *Coccidioides immitis* is given A hanging block preparation showed that it took from about seven to ten days for the mycelium to form into spherical or almost spherical spores. Tissues stained by the osmic acid method of Murray showed many interesting details. Some structures took the osmic acid stain and some took the contrasting stain. For convenience we called these types osmic-acid-positive and osmic-acid-negative. In some preparations we found that these two forms were contained in the same shell. This type had a large double-contoured membrane taking the contrasting stain, and the membrane was frequently spiculated and ruptured. Within this membrane were the osmic-acid-positive and osmic-acid-negative forms, which frequently were passing through the ruptured double-contoured membrane. Such structures as these suggest a bisexual life. In the previous report we noted that it took ten days for the animals to manifest any clinical symptoms. During the present morphologic study it was found that ten days was required for spore formation. Thus it would seem that it is the dissemination of the spores that is coincident with the spread of disease.

AUTHOR'S SUMMARY.

THE SIGNIFICANCE OF CERTAIN REACTIONS INDUCED BY "RESTING BACTERIA." ARTHUR ISAAC KENDALL and MITZUTERU ISHIKAWA, J. Infect. Dis. **44**:282, 1929.

The reduction of methylene blue by "resting bacteria" in the presence of certain carbohydrates is precisely paralleled by the fermentation of these same carbohydrates in cultural mediums inoculated with identical strains of proliferating bacteria. It is inferred that resting bacteria, therefore, initiate changes in substrates which they, as proliferating bacteria, would subsequently use for their energy requirements. The initial changes thus induced in substrates are not associated with the proliferation of the organisms; they occur under conditions of time, temperature and environment which preclude growth. The substrate, thus initially altered, is conceived of as in a state peculiarly adapted to rapid utilization for energy. The high degree of specificity of this preliminary change in various carbohydrates resides in the hereditary chemical architecture of the microbic protoplasm. It seems to be manifested at the surface of the microbe. The reactions induced by "resting bacteria" will not ordinarily supplant cultural reactions; the technic is more complex and cumbersome.

AUTHORS' SUMMARY.

FATAL SEPTICEMIA IN MAN DUE TO BACILLUS (SALMONELLA) SUIPESTIFER. JOHN T. BAUER and MARGARET MCCLINTOCK, J. Infect. Dis. **44**:292, 1929.

A fatal human infection suggesting typhoid fever and due to an organism with the cultural and serologic characteristics of *B. suipestifer* is described. The source of the infection remains undetermined.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF POSTMORTEM BACTERIOLOGIC EXAMINATION WITH SPECIAL REFERENCE TO STREPTOCOCCI AND ENTEROCOCCI. EMANUEL Z. EPSTEIN and M. A. KUGEL, J. Infect. Dis. **44**:327, 1929.

In these bacteriologic investigations at necropsy in the sixty-six blood cultures and sixty-two bone marrow cultures, at least one organism was always present. In forty-two heart muscle cultures, five were sterile, and in forty-three valve examinations four were sterile. Streptococci of all kinds were isolated in 79 per cent of the cultures of the blood, in 67 per cent of the bone marrow, in 47 per cent of the heart muscle and in 40 per cent of the normal valves. Nonhemolytic streptococci were found in blood, bone marrow, heart muscle or valve in 86 per cent of the cases. The infrequency of the pneumococcus, *streptococcus beta* and anaerobic organisms was observed. A strikingly high percentage of nonhemolytic streptococci tested were identified as enterococci. It seems that no significance can be attached to the recovery at necropsy of such organisms as *Streptococcus alpha, Streptococcus gamma,* enterococcus, *Staphylococcus aureus, Bacillus coli* and *Bacillus pyocyaneus* unless the same organism has been found during life.

AUTHORS' SUMMARY.

THE OCCURRENCE OF BACTERIUM TULARENSE IN THE WOOD TICK, DERMACENTOR OCCIDENTALIS, IN CALIFORNIA. R. R. PARKER, C. S. BROOKS and HADLEIGH MARSH, Pub. Health Rep. **44**:1299, 1929.

The recent occurrence in San Benito County, Calif., of an unrecognized pathologic condition in cattle heavily infested with ticks has resulted in the demonstration in adults of a natural tularemia infection due to the Pacific coast tick, *Dermacentor occidentalis* Newmann. This observation is of importance, because this tick, which is common in many sections of California and in southwestern Oregon, is a frequent parasite of man, and, hence, an apparent potential source of human tularemia. It has also been reported in horses, cattle, deer, dogs, sheep and rabbits. The data at hand are not sufficient to justify an assumption as to what part *B. tularense* might have played in the pathologic involvement of the affected cattle. They are of interest chiefly as further evidence of the wide dissemination of tularemia in nature and of the numerous avenues for human contact.

THE OXIDATION BY BACTERIA OF COMPOUNDS OF THE PARAPHENYLENDIAMINE SERIES. S. ELLINGWORTH, J. W. M'LEOD and J. GORDON, J. Path. & Bact. **32**:173, 1929.

The oxidations of the various methyl substitution products of paraphenylendiamine hydrochloride which may be produced by chemical oxidizing agents resemble closely those produced by certain bacteria. The facility with which such diamines are oxidized to colored products is increased as the number of methyl groups in the molecule is increased, and for this reason the tetramethyl compound is the most delicate reagent for indicating the oxidizing activities of bacteria. In the absence of free access of oxygen the various diamines appear to have a roughly similar toxicity for bacteria. When oxygen has free access to bacterial colonies previously exposed for a few seconds to a solution of a diamine, it is found that the monomethyl compound is the most toxic, and the teramethyl the least toxic, and the variation in toxicity is closely associated with the speed with which the colonies develop a black tint. The tetramethyl compound, which differs from the other diamines examined in not developing a black tint on oxidation, and which is less toxic on oxidation than the others, is the most suitable for use in diagnostic bacteriology. It should be used in a 0.5 per cent solution, which is the lowest concentration giving frank color reactions in bacterial colonies. The bacterial colonies capable of oxidizing the tetramethyl derivative to a blue-violet also reduce this compound, so that the color fades away again, although at varying speeds with different bacteria and most slowly in the case of those which oxidize it most rapidly. In the case of the other compounds oxidized in bacterial colonies to a black tint, the oxidizing colonies are picked out permanently, since the development of the black color coincides with the death of the bacteria, and there cannot therefore be any subsequent reduction. The tetramethyl compound indicates the oxidizing activity of a number of bacteria not picked out by the other diamines, notably *B. pertussis* and *B. influenzae*, of which the former is the most active. All attempts to prepare mediums containing paraphenylendiamines or modications of such substances, on which actively oxidizing bacteria would develop colored colonies as they grow, have failed.

AUTHORS' SUMMARY.

THE EFFECT OF CERTAIN FACTORS ON THE GROWTH OF THE PNEUMOCOCCUS. HEDLEY D. WRIGHT, J. Path. & Bact. **32**:203, 1929.

For full growth of the pneumococcus a small amount of fermentable carbohydrate (dextrose) is necessary (0.2 per cent). Excess leads to production of high acidity and so hastens autolysis. Thermostable nitrogenous substances are adequately supplied by 1 per cent peptone; relatively thermolabile constituents, essential to growth, are to be found in yeast extract and blood in large amount, in extract and in serum in small amounts, and also in peptone. Heating organic fluids, especially peptone, serum and yeast extract, causes them to become inhibitory to the growth of the pneumococcus. This inhibitory effect is diminished or its development is prevented by conditions favorable to reduction. The pneumococcus is also inhibited by excess of salts and readily destroyed by salts in the absence of colloids. Under certain conditions small quantities of calcium salts are favorable to growth. From a study of growth curves it is concluded that the length of the period of lag and the rate of growth depend on all the nitrogenous constituents of the medium and not solely on the so-called accessory factors.

AUTHOR'S SUMMARY.

THE EFFECT OF GROWING SMOOTH AND ROUGH CULTURES IN SERUM. J. A. ARKWRIGHT and R. M. PITT, J. Path. & Bact. **32**:229, 1929.

In nutrient broth diluted 1 in 5 with distilled water and in normal rabbit serum diluted 1 in 5, little effect in turning S cultures into R was detected even in old cultures. Culture mediums containing serum with somatic agglutinins for the S strain growing in them have a strong tendency to turn the S culture into the R

form, in the course of one or two weeks. This property is independent of the presence of flagellar agglutinins, and is exhibited whether the S somatic agglutinins have been produced by the organism in the culture (*B. typhosus*) or by another (*B. enteritidis*, Gaertner), so long as these agglutinins agglutinate the bacterium in the culture. The effect of an agglutinating serum on the production of the R form from the S form is not seen if the S somatic agglutinins have been removed by heating at 70 C. or by specific absorption with the appropriate bacterial emulsion. Neither growth in R serum nor growth in normal serum with or without a steamed S emulsion had the effect of transforming R into S cultures. Cultures with R somatic agglutinogen which formed S looking colonies and were not agglutinated by salt solution appeared in several old cultures, especially those which had been definitely R at some time; since these were R antigenically they should be regarded as essentially R. All the cultures were still motile at the end of the various experiments, though in several instances they had been growing in antiflagellar serums.

AUTHORS' SUMMARY.

TRYPSINIZED SERUM TELLURITE COPPER SULPHATE AGAR FOR THE ISOLATION OF CORNYEBACTERIUM DIPHTHERIAE. V. D. ALLISON and T. H. AYLING, J. Path. & Bact. **32**:299, 1929.

The addition of 0.05 per cent of copper sulphate to trypsinized serum tellurite agar increases its value in the isolation of *C. diptheriae* from nasal, throat and ear swabs. The action of the medium is as follows: The growth of staphylococci and streptococci is prevented; *C. diphtheriae, C. hofmannii* and organisms of the diphtheroid group grow out unrestricted, and are much more readily recognizable in cultures. The spread of organisms of the *B. proteus* type, so often present in swabs from the ear, is inhibited. The differential appearance of colonies of *C. diphtheriae, C. hofmanni C. xerosis* and other organisms of the diphtheroid group is more accentuated on this medium than on trypsinized serum tellurite agar. Cultures of *C. diphtheriae* on the medium produce a characteristic somewhat pungent odor. A series of swabs from acute cases of diphtheria was inoculated on to plates of the copper sulphate medium for the isolation of *C. diphtheriae;* the swabs were also inoculated on to slopes of Loffler's medium for the microscopic examination of stained films from the resultant cultures, owing to the atypical appearance microscopically of some strains of *C. diphtheriae* when grown on the copper sulphate medium. By this means it has been shown that the presence or absence of virulent *C. diphtheriae* may be reported within forty-eight hours from the receipt of the swab. Growth on the copper sulphate medium has no effect on the virulence of *C. diphtheriae.*

AUTHORS' SUMMARY.

HYDATID INFESTATION (ECHINOCOCCUS GRANULOSUS) IN SHEEP, OXEN AND PIGS, WITH SPECIAL REFERENCE TO DAUGHTER CYST FORMATION. N. HAMILTON FAIRLEY and R. J. WRIGHT-SMITH, J. Path. & Bact. **32**:309, 1929.

The distribution and incidence of degeneration in 6,497 sheep cysts, in 929 ox cysts and in 727 pig cysts are considered. Forty-three examples of early endogenous daughter cyst formation were studied in these hosts. Degeneration or rupture of the parent cyst was never observed, and the adventitia was normal in thirty-nine instances. The frequent incidence of degeneration noted in old mother cysts of large dimensions is essentially a secondary phenomenon due to increased intracystic tension occasioned by the growth of young endogenous daughter cysts. The present study constitutes the only series of observations dealing with the early stages of endogenous daughter cyst formation and the results are incompatible with the view that they originate under conditions menacing the life of the parasite. One hundred and sixty-two examples of exogenous daughter cyst formation were studied. The mother cyst was degenerated and ruptured in eighty (49.4 per cent). The adventitia was normal in 129 (79.6 per cent), sclerosed and thickened in 27

(16.6 per cent), and calcified in 6 (3.7 per cent). Exogenous cyst formation was found to be entirely independent of the adventitia. Such cysts are formed by a localized evagination of both layers of the mother cyst with constriction and fusion at the neck of the protrusion, and subsequent separation into the pericystic space. Three stages in the evolution of exogenous cysts are described, and the high incidence of degeneration of the original mother cyst is shown to depend on its mechanical separation from the adventitia by daughter cysts which as a result of local pressure produce the tessellation effects discussed in the text. The presence of intracuticular vesicles (pseudodaughter cysts) was described and specially studied in pig cysts where they were found to originate as hyaline degenerations of the laminated layer. Their presence was also observed in other hosts including man. In our opinion nonrecognition of the true nature of the intracuticular vesicle constitutes the basis on which the whole classic theory of the intracuticular origin of the daughter cyst has been founded. Cuticularization of the brood capsule as described by Dévé is confirmed. Our observations also support the main thesis of Dévé that the vesicular evolution of the scolex constitutes the most common and important source of endogenous daughter cyst formation.

AUTHORS' SUMMARY.

ON SEASONAL VARIATIONS IN BONY WEIGHT IN PULMONARY TUBERCULOSIS. M. KESAVA PAI, Tubercle **10**:212, 1929.

There seems to be a general agreement of weight curves in all parts of the world, the apparent differences being due to differences in climate between the localities where the observations are made. Extremes of heat and cold and dryness of the air cause a fall of weight, while a pleasant temperature like that of summer in colder countries and the cold season in the tropics produces a rise in the weight curve. Rains have no particular effect on body weight. The factors discussed in this paper have an important bearing on the location of sanatoriums in India. These should not be constructed in the plains, where the climate is hot, nor on the west coast, where it is both hot and moist. Also, too dry a climate may not be congenial. A moderate elevation with a cool summer and moist cooling winds during the hotter months is desirable.

H. J. CORPER.

CO-RELATION OF CALCIUM METABOLISM, PARATHYROID FUNCTION AND CHRONIC PULMONARY TUBERCULOSIS. PHILIP ELLMAN, Tubercle **10**:257, 1929.

The calcium content of the blood serum in pulmonary tuberculosis varies only within normal limits (from 9 to 12 mg. per hundred cubic centimeters). In cases responding favorably to treatment, the calcium content can be increased, but only within normal maximal limits. The administration of calcium or parathyroid must be continued over prolonged periods, if calcium retention is to be promoted. A combination of parathyroid extract with calcium lactate has proved as effective as any. Microscopic examination of the parathyroid glands in cases of pulmonary tuberculosis shows signs of increased functional activity. It is concluded that there is a definite relationship between pulmonary tuberculosis, on the one hand, and calcium metabolism and parathyroid function, on the other.

H. J. CORPER.

THE EARLY INFILTRATION AND ITS RELATION TO THE DEVELOPMENT OF PHTHISIS. H. V. MORLOCK, Tubercle **10**:267, 1929.

The development of phthisis from an apical lesion is uncommon. The "early infiltration" is described and particular emphasis placed on the acute commencement of the disease and the possibility of mistaken diagnosis at this stage. The early infiltration may be a transient condition, healing to leave only a scar, which may later be discovered and considered to be the early manifestation of the disease,

but which, in fact, is the end-result of an attack of pulmonary tuberculosis. The "early infiltration" is often progressive, and when it has advanced, the condition of the lungs is then indistinguishable from phthisis.

H. J. CORPER.

LIVING TUBERCLE BACILLI IN A SEPTIC TANK EFFLUENT. S. LYLE CUMMINS and C. M. ACLAND, Tubercle **10**:310, 1929.

Living tubercle bacilli were found in the effluent from a septic tank, indicating the ability of these organisms to resist the digestive processes of this procedure.

H. J. CORPER.

INFLAMMATIONS OF THE PLACENTA AND FETAL SEPSIS. FRIEDRICH WOHLWILL and HANS ERHARD BOCK, Arch. f. Gynäk. **135**:271, 1929.

Four cases of diffuse placentitis are described. The bacteria were *Bacillus coli* in two cases; streptococci in one case; and a mixed infection of gram-negative bacilli (*B. coli*) and gram-positive anaerobic bacilli in the fourth case. The pregnancies concerned were in the fourth and fifth month. The placentitis is regarded as secondary to fetal bacteremia. The organisms were distributed in large quantities in the placenta, especially the villous vessels which contained emboli of bacteria; other fetal organs as the liver, spleen and brain also contained large numbers of bacteria. The organisms in the villi had invaded the intervillous spaces through a break in the syncytial lining and thus infected the maternal blood stream. One mother died of sepsis which was considered secondary to the fetal septicemia, and another mother whose uterus was removed showed that the organisms had extended into the vessels of the broad ligaments. In the two other cases there were no or slight reactions in the maternal organism despite the diffuse distribution of bacteria in fetuses. One of these had an external thoracic defect which probably permitted direct entrance of organisms from the infected amniotic water. The case of streptococcal fetal infection was considered to be secondary to a maternal focus. The other cases are thought to have been infected through the amniotic water, and the latter was thought to have been infected secondary to criminal interference with pregnancy. The reactions of the fetus and its ability to cope with infection are discussed. The placenta showed an accumulation of countless leukocytes about the villi, chorionic plate and about the amnion. There were regressive and progressive changes and phagocytosis. Despite the overwhelming distribution of bacteria in many of the other fetal organs, no reaction was visible except in the liver about the vessels containing the organisms. There was also some accumulation of histiocytes. In a note mention is made of five more cases of fetal bacteremia occurring in fetuses of three to five months. Bacteria were found in the bronchi and gastro-intestinal tract of one fetus of only three months' development, showing that even in this early state infected amniotic water can be aspirated or swallowed.

A. J. KOBAK.

RETICULO-ENDOTHELIAL SYSTEM IN LEPROSY. H. G. RIECKE, Beitr. z. path. Anat. u. z. allg. Path. **80**:201, 1928.

The rarity of leprosy in Germany prompted the author to study and report a fatal case in a woman, aged 28. The lesions of the skin were of the tuberculous type; tissue obtained from them during life was studied. Numerous nodular lesions were present in the mucous membranes of the nose, mouth and pharynx, and the larynx was diffusely involved. The liver and the spleen contained the characteristic nodules. The spleen revealed myeloid transformation of the pulp, and many lepra cells. The lymph nodes were hyperplastic and contained large reticulo-endothelial cells filled with lipoid material. The lepra cells, whenever present, were of the same size and morphology as the reticulo-endothelial cells and were filled with bacilli, but contained little or no lipoid. The storage of lipoid by the reticulo-endothelial cells is considered evidence of an abnormal lipoid metabolism in leprosy.

O. T. SCHULTZ.

ETIOLOGY OF INGUINAL GRANULOMA. A. MUSGER, Beitr. z. path. Anat. u. z. allg. Path. **80**:257, 1928.

From local tissue removed by biopsy and from pus, in a case of inguinal granuloma, Musger isolated a pseudodiphtheriod bacillus, which he obtained also from the blood of the patient. A similar organism was later obtained from the blood and inguinal nodes of a second patient. When inoculated locally in guinea-pigs, the organism caused changes in the inguinal lymph nodes similar to those in the nodes in man.

O. T. SCHULTZ.

THE PATHOLOGY OF ACUTE DISSEMINATED MILIARY TUBERCULOSIS OF THE LUNGS. W. GRETHMANN, Beitr. z. Klin. d. Tuberk. **71**:1, 1928.

The microscopic structure of miliary tubercles is largely dependent on the degree of immunity. Neither the clinical observation nor the histologic criteria can definitely establish the duration of the disease. Vascular foci are found in not more than from 70 to 80 per cent of the cases. They may rupture into the blood stream. The tubercles in the intima contain usually not many tubercle bacilli. Their significance as sources of the dissemination is doubtful. The pathogenesis of miliary tuberculosis is still obscure. The author protests against Huebschmann's theory that all miliary tubercles start with a miliary caseous pneumonia, and may then show productive changes. The miliary tubercle develops in the blood vessel wall, and residues of the latter are usually found in its center. Most of the tubercle bacilli are found where nuclear debris is seen. The alveolar epithelial cells play an important rôle in the formation of the tubercle; they are transformed into epithelioid cells. This paper contains many good illustrations and complete clinical and pathologic data.

MAX PINNER.

TUBERCLE BACILLI IN HEN'S EGGS. RAEBIGER, Beitr. z. Klin. d. Tuberk. **71**: 209, 1929.

Three chickens were infected with avian tubercle bacilli. Three days after the infection tubercle bacilli could be isolated in pure culture from the blood stream. Twelve eggs which were laid from ten to fourteen days after the infection were examined microscopically and culturally for the presence of tubercle bacilli. Fifty-two other eggs laid between the seventeenth and sixtieth day following the infection were examined only microscopically. The earliest date at which tubercle bacilli could be demonstrated in eggs was ten days after the infection. In all of the first twelve eggs tubercle bacilli could be demonstrated either microscopically or culturally. Out of the fifty-two eggs which were examined only microscopically, in nineteen or 36.5 per cent, tubercle bacilli could be demonstrated. Artificially infected eggs were boiled, and it was ascertained that avian tubercle bacilli may survive a five minute boiling period.

MAX PINNER.

EXPERIMENTS ON THE PRODUCTION OF TUBERCLES AND TUBERCULOID STRUCTURES IN THE SKIN OF HEALTHY PIGS FOLLOWING THE INJECTION OF LIPOIDS. A. HAIM, Beitr. z. Klin. d. Tuberk. **71**:269, 1929.

This is a complete report on extensive experiments which cannot be reported briefly. The main conclusions are that under certain conditions tubercle bacillus lipoids may produce typical tubercles in the skin of pigs. Other lipoidal materials and certain colloidal materials may produce similar lesions. Striking individual differences were observed.

MAX PINNER.

SPONTANEOUS TUBERCULOSIS IN MONKEYS. H. H. KALBFLEISCH and A. NOHLEN, Beitr. z. Klin. d. Tuberk. **71**:336, 1929.

This study was undertaken in order to establish the possible sources of error in experimental tuberculosis with monkeys. Both from their own experiments and

from an extensive review of the available literature, the authors conclude that monkeys living wild under normal conditions never contract tuberculosis. The frequency of tuberculosis in monkeys living in captivity depends on many different factors such as, crowding, uncleanliness, possible sources of infection, the amount of air currents, etc. Monkeys living in captivity are undoubtedly susceptible to tuberculosis, particularly if coresidence with an infected animal exists. The diagnosis of tuberculosis during the life time of monkeys can be done by clinical and roentgenologic observation. The roentgenologic data are important and reliable. Strictly extrapulmonary lesions occur only rarely, if ever. Tuberculin tests are unreliable, since tuberculous monkeys do not react essentially differently from normal monkeys. It was found that by keeping monkeys in the open air, even during cold periods in the moderate climate of Germany, the danger of infection was much decreased as compared with monkeys kept in stables. Spontaneous infection can be completely avoided if monkeys are kept in the open air and if all possible sources of infection, particularly infected animals are excluded.

MAX PINNER.

Immunology

THE AVIAN, HUMAN, AND BOVINE TUBERCULIN REACTIONS IN CHILDREN. B. M. GASUL, Arch. Pediat. **46**:67, 1929.

The conclusions are that 110 children with pulmonary tuberculosis, all of whom reacted positively to the human and bovine tuberculin, failed to react to the avian tuberculin with the usual Pirquet test. No appreciable differences were noted in the reactions to the human and bovine types. The avian tuberculin appears to be specific only to tuberculosis caused by the avian type of tubercle bacillus.

AUTHOR'S SUMMARY.

THE PRECIPITABLE SUBSTANCES OF BACILLI OF THE SALMONELLA GROUP. J. FURTH and K. LANDSTEINER, J. Exper. Med. **49**:727, 1929.

Specific precipitable substances rich in carbohydrates, containing little protein and small amounts of a material apparently of fatty nature, have been prepared from the main serologic types of the typhoid-paratyphoid groups. The preparations in their present state of purity do not exhibit pronounced chemical differences in spite of serologic dissimilarity. In this respect the results differ from those observed with the polysaccharides of pneumococci. The specificity of the precipitin reactions of these substances parallels, in a general way, the so-called small flaking agglutination. Attempts to separate different fractions from the active substance serologically by means of precipitation with antibody solutions were, on the whole, unsuccessful. The differences in resistance to the action of acid and alkali were found to be characteristic for various specific carbohydrates.

AUTHORS' SUMMARY.

THE MECHANISM OF OPSONIN AND BACTERIOTROPIN ACTION. STUART MUDD, BALDUIN LUCKÉ, MORTON MCCUTCHEON, MAX STRUMIA and EMILY B. H. MUDD, J. Exper. Med. **49**:779, 797 and 815, 1929.

1. Methods are described for investigating the relation between phagocytosis of bacteria by polymorphonuclear leukocytes and certain physicochemical properties of the bacterial surface. Serum sensitization causes the following changes in the properties of acid-fast bacteria: increased cohesiveness, decrease in surface electric potential difference, decrease in the power of the bacteria to become wet by oil and increased phagocytosis. Tests have been conducted periodically with the serums of four rabbits under active immunization, with as many strains of acid-

fast bacteria; the parallelism between the alteration in bacterial surface properties and the promotion of phagocytosis by these serums have been, within the experimental error, complete. The percentage of phagocytosis of a given bacterial suspension has been found to depend both on the sensitizing serum component or components deposited on the bacterium and on the intrinsic properties of the unsensitized bacterial surface.

2. The combination of a substance or substances present in fresh immune rabbit serum, heated or unheated, or in fresh unheated normal rabbit serum, with a substance or substances in the bacterial surface, causes an increase in cohesiveness, a decrease in surface potential difference and a characteristic alteration in wetting properties of the bacteria, and prepares the bacteria for phagocytosis. The effective substance or substances in the serum may become so altered as the result of heating or aging that combination with the bacterial surface, while causing changes in bacterial surface properties indistinguishable by the present physicochemical tests from these just mentioned, may not lead to phagocytosis, or may lead to phagocytosis with a prezone not paralleled by a prezone in the changes in surface properties. Sensitization of bacteria with human serums causes changes in surface properties similar to those caused by rabbit serums, but does not lead to phagocytosis by rabbit leukocytes. The spreading requirements of rabbit polymorphonuclear leukocytes are evidently highly selective.

3. Rabbits infected intravenously with virulent mammalian tubercle bacilli have, in a majority of cases, developed circulating antibodies to a slight but appreciable degree. The increase in titer was detected in one group of rabbits within the second or third week, and in others during the second month, of infection. In rabbits with residual pulmonary foci, resulting from infection six months or more previously with human tubercle bacilli, on reinfection with bovine tubercle bacilli circulating antibodies developed promptly, strikingly in excess of those found during the course of primary infection. Such antibodies were present six or seven days after reinfection. The changes in titer during tuberculous infection, as detected by the bacterial surface reactions and by phagocytosis, were again, within the experimental error, in quantitative correspondence. The loss of the phagocytosis-promoting power in heated normal serum involves an exception to this correspondence between surface and phagocytosis effects. This exception was discussed in an earlier paper.

AUTHORS' SUMMARY.

THE INFLUENCE OF CHEMICAL AND OTHER AGENTS UPON THE TOXICITY AND ANTIGENIC POWER OF RICIN. EMMETT B. CARMICHAEL, J. Pharmacol. & Exper. Therap. **35**:193 and 223, 1929.

The preparation of several specimens of ricin is described. These exhibited such characteristic properties as coagulation by heat, toxicity when injected into animals and agglutination of mammalian blood corpuscles. The toxicity of ricin was destroyed by such oxidizing agents as potassium permanganate, 30 per cent hydrogen peroxide, ozone, chlorine, bromine and iodine. Ultraviolet light, particularly that with wave lengths between 225 and 250 millimicrons, was found effective in destroying the toxicity of ricin. Ricin detoxified by boiling or by partial oxidation with potassium permanganate retains its antigenic activity, so that serums of rabbits and guinea-pigs receiving injections of detoxified ricin protect white mice from fatal doses of untreated ricin. Prolonged treatment of ricin with a large excess of potassium permanganate destroys its antigenic power as well as its toxicity. A single large dose of ricin detoxified with potassium permanganate develops an immunity in rabbits strong enough to protect them from as many as 120 lethal doses of the untreated ricin. Serums from these rabbits in amounts as small as 0.25 cc. protect white mice against fatal doses of ricin. The antigenic activity of ricin is thus found to be less susceptible to oxidizing agents, such as potassium permanganate, than is its toxicity.

ARTHUR G. COLE.

IMMUNITY TO TUBERCULOUS SUPERINFECTION. BRUNO LANGE, Ztschr. f. Hyg. u. Infectionskrankh. **110**:185, 1929.

After carefully weighing all available evidence, Lange comes to the following conclusions: The experimental experiences and the observations in man show, beyond doubt, that a specific immunity develops in the course of active tuberculosis. The Behring-Römer doctrine of the acquired immunity of adults due to childhood infection is not sufficiently supported by experimental, epidemiologic or other evidence. In order to obtain a better judgment of the action of superinfection in man, additional experiments are necessary which approximate, as much as possible, the conditions existing in primary infection and superinfection in man. So far as the primary infection is concerned, this means the artificial production of an active infection which remains latent for a long time and tends to heal. In the case of superinfection, attention should be paid to the conditions normally present, such as infection with minimal doses and the variations of natural susceptibility which are so important in the course of the disease. A proper experimental investigation of the effect of the complex factors which lower resistance seems to be possible only when by additional experiments one is more thoroughly informed of the exact modification of an infection by a preceding one under conditions which exclude these complicating factors.

W. OPHÜLS.

Tumors

MULTIPLE SUPERFICIAL BENIGN EPITHELIOMA OF THE SKIN. F. WISE, Arch. Dermat. & Syph. **19**:1, 1929.

The disease designated by Little as erythematoid benign epithelioma, in 1923, has for many years been recognized in this country as multiple, benign, superficial epithelioma of the skin. The lesions are usually basocellular new growths, arising primarily on unchanged skin; they may also be prickle cell lesions or mixed growths. Lesions of this kind have been confused with Bowen's disease, extramammary Paget's disease and (more rarely) arsenical epitheliomas and keratodermas. In microscopic preparations, Bowen's disease is a distinct entity with histologic features peculiar to itself and like any intra-epidermic carcinoma. The exact status of extramammary Paget's disease is still undetermined both clinically and histologically. Although the clinical diagnosis of multiple benign superficial epithelioma usually is not attended with many difficulties, the differentiation from Bowen's disease, extramammary Paget's disease, arsenical keratodermas and other lesions which closely simulate the multiple new growths is by microscopic examination of the lesions.

AUTHOR'S SUMMARY.

THE LYMPHOBLASTOMAS. H. L. KEIM, Arch. Dermat. & Syph. **19**:533, 1929.

The results in twenty patients with lymphoblastoma, including complete postmortem studies in ten, are recorded. There is a striking variability of the clinical changes in this group of diseases, making proper classification extremely difficult. That seemingly widely divergent dermatoses are genetically related is established by the striking similarity of the microscopic picture. In each there are tumor cells of the lymphocyte series resting in a connective tissue reticulum, the distinguishing feature occurring in the degree of differentiation of the cells of the neoplasm. The term lymphoblastomas is given to the members of this group on the basis of their genetic relationship.

AUTHOR'S SUMMARY.

CANCER OF THE SKIN DUE TO OCCUPATION. W. J. O'DONOVAN, Arch. Dermat. & Syph. **19**:595, 1929.

The author cites the cases of eighteen patients with carcinoma who were in the tar industry, three in an anthracene factory, three with arsenic cancer of occupational origin, one oil carcinoma and one x-ray carcinoma. Sixty-one patients

with carcinoma of the hands are mentioned, and an effort is made to correlate the condition with the occupation of the patient.

A Unified Explanation for New Growths on Man. Heinrich Müller, Virchows Arch. f. path. Anat. **269**:105, 1928.

A study of the literature, much thought and the results of careful study of many tumors, especially in relation to their growth and spread, led Müller to the following opinion: Carcinoma is regeneration gone wrong. Physiologic regeneration is stimulated either by the products of destruction of tissue or by a hormone coming from another organ. He points out that stimulation of new growths by hormones may occur, e. g., the growth of bones, hypertrophy of the breast during pregnancy, development of secondary sex characters, etc. These hormones, he argues, are specific. The tissue formation occurs through the mesenchyme tissues which are present throughout the entire body and which in part are in close relation to the vascular system. The replacement of tissues destroyed is overdone, but after proper replacement, it gradually regresses to the proper point. This replacement begins in the mesenchyme in long continued destruction or even in sudden destruction as by trauma and roentgen effect. Carcinoma may occur from increased regeneration which then continues as an independent regenerative process. This prolonged action is caused by a prolonged destruction of tissue manifestly due to insufficient blood supply. Histologic studies have shown that the capillaries concerned in regeneration (carcinoma) at first show an increase in size; finally, they are compressed by the epithelial cells and obstructed. The cellular damage leads to further release of hormones, which leads to further stimulation of growth. The formation of metastases occurs through hormones carried through the lymph and blood stream. It is easily understood why the lymph nodes in the line of drainage in a primary carcinoma should be involved since they receive the lymph containing the released hormones from the primary growth. The predilection of the liver may be explained by its slow blood stream rate and prolonged activity of hormones. The fact that in many cases there is a predilection of organ systems for the formation of metastases may be explained by the assumption of specific sensitivity of their mesenchyme to the oncoming organ hormones.

This point of view differs from most others in that it disregards the hypothetic changes in character of the carcinomatous cells and allows a physiologic interpretation. Naturally, in pathologic anatomy one sees things as they are, or rather were, when the tissues were removed, and the dynamics of the processes cannot be studied.

V. C. Jacobson.

The Effect of Diet on Tumor Growth (Experiments with Rat Sarcoma). E. Friedberger and I. Grünstein, Ztschr. f. d. ges. exper. Med. **62**:344, 1928.

Tumor growth is influenced by disturbances of nutrition in the sense that insufficient or deficient diet retards tumor growth. This is equally true when the quantity of food is insufficient and when the quality of food is at fault (vitamin deficiency through heating, insufficient quantity of mineral salts, etc.).

Conversely, excessive food favors tumor growth. The authors emphasize that the influence of diet on neoplastic growth was known to the ancients and in medieval times, but appears to have been forgotten in modern times. They give an extensive bibliography dealing with the clinical as well as the experimental phases of the subject.

Balduin Lucke.

The Significance of Atrophy and Regeneration in Experimental Tar Cancer. A. R. Jonkhoff, Ztschr. f. Krebsforsch. **26**:25, 1928.

Studies of the successive epithelial developments in the production of tar cancer in white mice gave the following stages: (1) periods of excessive growth of hair

alternating with intervals of absence of hair; (2) the appearance of papillomas in connection with growth of hair; (3) possible disappearance of these papillomas; (4) definite tumors, eventually becoming malignant, appearing only in the later stages of growth of hair, and (5) increasing atrophy and disappearance of hair and other accessory structures of the skin. Epithelial malignancy appears to be the sequel of associated atrophy and regeneration, and does not occur until the former has become pronounced.

H. E. Eggers.

Roentgen Carcinomas in Mice. A. R. Jonkhoff, Ztschr. f. Krebsforsch. **26**:32, 1928.

Of six mice subjected to prolonged irradiation with the roentgen rays, tumors developed in four. In one the tumor was definitely carcinomatous; in the others it took the form of a carcinoma sarcomatoides, which, however, the writer regards as of truly epithelial derivation for the following reasons: Occasionally, the epithelial cells could be seen taking the spindle shape of those of the tumor; the tumor cells could be seen gradually blending into epithelial cells; in sites where tumor had not developed, there was cutaneous atrophy similar to that seen in the development of tar cancers, and in one of the animals there were pulmonary metastases which showed epithelial cornification. Long latent periods were observed in all the mice.

H. E. Eggers.

Sarcoma of the Pericardium. D. M. Chajutin, Ztschr. f. Krebsforsch. **26**:72, 1928.

The writer reports a case of primary spindle cell sarcoma of the pericardium. In the literature he was able to collect only seven well established cases in addition to his own. Of the six reported cases in which the sex was given, only one was in a female. These tumors occurred predominantly at an early age.

H. E. Eggers.

A Connective Tissue Mixed Tumor of the Female Breast. S. Kurosu, Ztschr. f. Krebsforsch. **26**:99, 1928.

A detailed description is given of a mixed tumor of the breast, with a composition summarized by the following designation: fibrochondro-osteo-angiosarcoma. A number of similar cases have been reported previously — with sufficient frequency to warrant their designation as connective tissue mixed tumors of the breast. The author regards the various elements as resulting from metaplasia rather than from displacement.

H. E. Eggers.

Medicolegal Pathology

Carbon Monoxide as a Tissue Poison. J. B. S. Haldane, Biochem. J. **21**:1068, 1927.

There have always been at least two explanations of the way carbon monoxide exerts its poisonous action, and for a long period one of them has maintained a definite supremacy in its general acceptation. This is the well known theory of anoxemia, that by reason of the great affinity of carbon monoxide for hemoglobin, the oxygen is replaced, and that all the subsequent chemical, functional, structural and other alterations which may follow in the wake of carbon monoxide poisoning owe their origin solely to this deprivation of oxygen. A vast amount of experimentation, much of it with physical chemistry applied to biology, has strongly supported this theory. The other theory, without minimizing the importance of anoxemia and the rôle played by hemoglobin, also advocates that CO is a direct tissue poison.

In spite of the little experimental proof that it has received, this last view has been resolutely defended by a few to whom the observations recorded in this

article by Haldane probably afford considerable relief. By the use of moths and seeds of water cress (*Lepidium sativum*), hemoglobin was excluded; rats were also used. All the results point to the ability of CO to lessen or inhibit oxidation by catalytic substances that unite with CO instead of O_2. For example, a rat with presumably all its hemoglobin occupied by CO and kept alive by increasing the partial pressure of O_2 was quickly killed with more CO, but not with an inert gas such as N_2.

Haldane suggests that tissues probably contain several catalysts with different affinities for CO and O_2 and exhibiting different behaviors with variations of the partial pressures of CO and O_2. He also announces that CO in sufficiently strong concentrations, no matter how made, has an odor like garlic, and to one of his colleagues like tar. A number of procedures carried out to abolish the odor were unsuccessful. Usually CO is described as an odorless gas.

E. R. Le Count.

The Danger of Intravenous Administration of Electrargol. E. Quater and B. Lewitin, Zentralbl. f. Gynäk. **51**:2803, 1927.

After several intravenous injections of this colloidal solution into two patients with severe puerperal fever, symptoms regarded as anaphylaxis developed almost at once after another dose. There was difficulty in breathing, cyanosis, a rapid or undetectable pulse, a chill with severe shivering and other symptoms of profound shock. Both women finally recovered. One death has been observed. The authors succeeded in producing similar effects experimentally in one of two guinea-pigs, but only after a number of intracardiac injections.

E. R. Le Count.

Death from Hemorrhage as a Sequel of Miscarriage. F. Federlin, Zentralbl. f. Gynäk. **51**:3068, 1927.

Severe or fatal hemorrhage is said to follow designedly interrupted pregnancy more often than spontaneous miscarriage. Since Neu (Ist die Blutung beim Abort eine Indikation zur sofortigen Entleerung des Uterus, *München. med. Wchnschr.* **67**:1350, 1920) stated a few years ago that death from hemorrhage as a sequence of miscarriage was practically unknown, eighteen such deaths have been reported. To these, Federlin adds one, that of a married woman subject to metrorrhagia and to intermenstrual periods of from six to eight weeks. She therefore did not know she was about three months pregnant. She had bled so much that she was admitted to the hospital practically pulseless, and died in a few hours. Little influence on the laxness of the uterus was exerted by remedies that cause uterine contraction. The placenta and fetus lay loose in the uterus, and no bleeding took place when they were removed. No wound or other injury of the uterus or vagina was found after death.

E. R. Le Count.

Gangrene of the Legs Following Abortion. G. V. Páll, Zentralbl. f. Gynäk. **51**:3246, 1927.

This form of gangrene is due to bacterial arteritis and thrombosis of the femoral artery or of some of its divisions. The infection starts in the uterus. About sixty cases are reported, in which there were thirty deaths without amputation and eighteen recoveries after amputations in twenty-four patients. The woman cared for by Páll died about thirty-six hours after the entire right leg became gangrenous from an obturating clot high up in the femoral artery. Hemolytic streptococci were recovered from the blood during life. The abortion was criminal and at the third month of gestation.

E. R. Le Count.

Postmortem Examinations and Accident Insurance. W. di Biasi, Aerztl. Sachverst.-Ztg. **35**:27, 1929.

Five cases are mentioned briefly: (1) prostatic carcinoma with metastatic tumors in the bones and lymph glands demonstrated as the cause for a death which,

it was claimed, was the result of an injury of the chest followed by pulmonary tuberculosis; (2) necrosis of the hands, said to have resulted from freezing, which was found to have its cause in changes of the spinal cord due to anemia; (3) edema and passive hyperemia of the lungs from fibrous myocarditis and cardiac dilatation, which was confused during life with asthma from dust; (4) ascending renal infection from fractured pelvic bones and a torn urethra, disclosed by a post-mortem examination as the cause of death after liability had been denied; (5) a claim that a broken back and its sequels had caused death, which it was found had been caused by a primary cancer of the lung.

E. R. Le Count.

Hemorrhage at the Base of the Brain from Ruptured Aneurysms of the Cerebral Arteries. E. Pawlowski, Aerztl. Sachverst.-Ztg. **35**:65, 1929.

Since the study of Charcot and Bouchard, almost a century ago, spontaneous intracerebral hemorrhage has been ascribed to rupture of miliary aneurysms of small arteries or arterioles due to sclerosis or patches of necrosis in the vessel walls. The arteriosclerosis is generalized and associated with nephritis, hypertension and hypertrophy of the heart, all developing in the middle or later decades of life. The aneurysms discussed by Pawlowski are altogether different. They

Distribution of 397 Aneurysms of Large Intracranial Arteries

Arteria fossae Sylvii	92	Arteria cerebri posteriori	14
Arteria basilaris	83	Arteria cerebri anteriori	10
Arteria caroticis interni	60	Arteria meningea media	5
Arteria communicans anterior	42	Arteria cerebelli inferiori	4
Arteria corporis callosi	26	Arteria arachnoidea	3
Arteria communicans posterior	20	Arteria ophthalmica	3
Arteria cerebri medii	16	Arteria cerebri superiori	2
Arteria vertebralis	15	Multiple vessels	1
Vessel anomaly	1		

occur at all ages, and hypertension, arteriosclerosis, etc., do not accompany them with any constancy. Explanation of these aneurysms of the larger subdural or intraleptomeningeal arteries has been difficult. Mechanical factors connected with the arrangement of these vessels, the way they branch, absence of much support from adjacent structures, congenital anomalies in them and thinness of their walls have all been suggested; also that with any one or more of such factors actively concerned the relatively high blood pressure in the cerebral arteries and their short distance from the heart are important aids to the development of the aneurysms.

It is commonly held that syphilis is remotely concerned with their origin, or altogether without any influence. Some authorities favor trauma as the cause, and point out the many irregularities about the clinoid processes of the sphenoid bone, the elevations on the clivus, the way the vertebral and other arteries may be bruised by the edges or rims of bony openings or passages in which they course. To these are added the strain put on the vessels when the head is injured and the brain with the fluid in and about it is jolted back and forth, and the pull made on the vessels when the rounded contour at different places in the cranium is flattened or the cranial bones are broken.

Pawlowski refers to two investigations of conditions intimately related to the cause of these aneurysms. One of them was reported recently by Forbus (*Centralbl. f. allg. Path. u. path. Anat.* **44**:243, 1929) and dealt with congenital defects in the muscular layers of arteries in many parts of the body. He found them in twenty-

five of thirty-one apparently normal cerebral arteries. Pawlowski believes aneurysms may easily form in such weakened places when they are bruised or slightly torn by muscular strains. The other (Reuterwall, O. P.: Ueber bindegewebig geheilte Risse der Elastica interna der Arteria basilaris, Stockholm, 1923), was a systematic examination of the large arteries at the base of the brain, which resulted in the finding of many scars resembling healed lacerations in their walls. These two researches are, in a way, complemental, since they possess a common end: weak regions in the vessels where saccular outpouching may readily occur. For three of the nine deaths which Pawlowski adds to others (397 in all) from rupture of such aneurysms, he obtained a history of injury. The frequency with which the aneurysms are located on certain arteries, according to the table accompanying his discussion, is slightly different from that found by Szekely (*Beitr. z. gerichtl. Med.* **8**:162, 1928), whose summary is not included with those of several others in the table. The statistics of both authors comprise altogether 554 aneurysms, which means death from rupture of these aneurysms in 554 persons. persons.

E. R. Le Count.

Technical

The Sedimentation Test in Pulmonary Tuberculosis. H. A. Clegg, Tubercle **10**:205, 1929.

The normal sedimentation rate by the Zeckwir and Goodel method, in which 2 cc. of 3 per cent sodium citrate and 8 cc. of blood in a 15 cc. centrifuge tube are used, was 9.6 cc. red cells at one hour. In the cases of normal sedimentation investigated, the physiologic variation was slight. The sedimentation rate in pulmonary tuberculosis appears to be an accurate measure of the activity of the lesion, and, as an additional clinical test, is of use in forming a diagnosis and prognosis. The test is of more use in prognosis than in diagnosis, and has not yet proved of value in early cases. Active cases investigated showed an abnormal rate of sedimentation. Several observers have found a normal sedimentation rate in active pulmonary tuberculosis, thus differing with the author and with Westergren whose observations were based on 72 and 340 cases, respectively. There is general agreement as to the utility of the test in relation to clinical observations.

H. J. Corper.

Celluloid Plates for Mounting Museum Preparations. H. Merkel, Centralbl. f. allg. Path. u. path. Anat. **45**:38, 1929.

Merkel favors celluloid plates instead of glass, especially for sections of the brain, because they can be cut easily with a knife or scissors in thicknesses up to 1.5 mm., are transparent, or can also be obtained in white or black to afford contrast, and can be easily perforated to permit the passage of retaining threads.

George Rukstinat.

Postmortem Examination of the Head of New-Born. Erik Rydberg, Acta path. et microbiol. Scandinav. **6**:145, 1929.

The bones of the cranial vault are carefully separated from the parietal dura, and removed piecemeal. The dura is then examined and removed sufficiently so that the brain can be taken out in the usual way, except that the brain-stem is cut across, so that the tentorium and the contents of the posterior fossae can be examined thoroughly. The advantages of the method are that extravasations of blood over the surface of the brain can be studied satisfactorily in situ without the admixture of blood set free during the opening of the skull; the veins that open into the longitudinal sinus can be followed easily; the tentorium can be examined in situ, and the brain removed without damage. The disadvantage of the method lies in the fact that the bones of the vault are removed piecemeal; hence successful restoration of the head is rather difficult.

Book Reviews

PROTOZOOLOGY. A MANUAL FOR MEDICAL MEN. By JOHN GORDON THOMSON and ANDREW ROBERTSON. Cloth. Price, $11. Pp. 376. New York: William Wood & Company, 1929.

This latest addition to the rapidly increasing number of protozoological texts claims uniqueness in that it is written for the medical men of the tropics and is not solely a zoological treatise. Following an introduction of ten pages dealing with the fundamental structure and division of the metazoan and protozoan cell, the main portion of the book (268 pages) is devoted to the consideration of the protozoan species of medical importance. Seven sections (fifty-five pages) are then devoted to forms the systematic position of which is doubtful, such as the sarcocysts, various intracellular bodies (*Anaplasma, Bartonella,* etc.), the toxoplasmas, the spirochetes and the spirillum of rat-bite fever. The final sections contain a discussion of laboratory technic (twenty-four pages), a glossary of derivations and definitions (six pages) and references (three pages).

The various sections are not encyclopedic, but the main facts are carefully selected. In line with this method of condensation, comparatively few references to original authors are given in the text, and the bibliography is largely a list of texts and special monographs. Similarly, the treatment of various purely zoological questions, such as nomenclature, is reduced to a minimum, but questions such as those of cultivation, diagnosis and pathology are treated in a well rounded manner. The authors are particularly to be commended on their inclusion of such sections as "Fallacies and Puzzles in Blood Examination" and "Common Objects in the Stools Other Than Protozoa," which serve to warn the student against many of the pitfalls of diagnosis. Furthermore, the material in the main sections is admirably selected, and consists, in general, of accurate morphologic accounts of the parasites, their life history, methods of diagnosis and, in the case of the pathogenic protozoa, the pathology of the resulting infections. The detailed account of the pathology is the unique feature of the work and should be especially appreciated by medical students, for whom it is primarily intended. Although the main emphasis is placed on the forms living in man, considerable attention is given to such parasites of animals as the Texas fever organism, *Trypanosoma lewisi* and many others.

The entire treatment reflects the judgment of authors with long teaching experience who are well versed in the advances made by recent investigators. In the reviewer's opinion, the book is well adapted for the particular class of students for which it is intended. It is not intended for, nor will it fill the needs of, more advanced students or specialists as well as some of the other textbooks of protozoology.

The volume is excellently printed, illustrated and indexed. Among the illustrations are four superbly colored plates and a large number of photomicrographs. Many of the latter are admirable, but some hardly enhance the value of the work and might have been either omitted or replaced by simpler drawings.

BRAIN MECHANISMS AND INTELLIGENCE. A QUANTITATIVE STUDY OF INJURIES TO THE BRAIN. By K. S. LASHLEY. Price, $3. Pp. 184. Chicago: The University of Chicago Press, 1929.

This is the first volume of a series of monographs on the work of the Behavior Research Fund in Chicago, which was inaugurated to conduct research in problems of human behavior. The influence of varying grades of cerebral destruction in the white rat was studied for a variety of functions. The list of chapter headings is illuminative of the scope of the work: theories and problems; general methods; the influence of cerebral lesions on the capacity to learn; the influence of cerebral

injuries on retentiveness; the course of learning in deteriorated conditions; the effects of cerebral lesions subsequent to the formation of the maze habit: localization of the habit; the relation of reduced learning ability to sensory and motor defects; discussion of experimental results; the nature of deterioration following cerebral lesions; comparison of the rat with other forms; the neural mechanisms in adaptive behavior. It concerns in fact a new and noteworthy experimental approach to the study of cerebral physiology. The style is clear and concise. There are thirty-three figures in the text, eleven of which are plates with diagrams of lesions in the different series of experiments, and a select bibliography. The following inferences are drawn by the author from his results:

"The learning process and the retention of habits are not dependent upon any finely localized structural changes within the cerebral cortex. The results are incompatible with theories of learning by changes in synaptic structure, or with any theories which assume that particular neural integrations are dependent upon definite anatomical paths specialized for them. Integration cannot be expressed in terms of connections between specific neurons.

"The contribution of the different parts of a specialized area or of the whole cortex, in the case of nonlocalized functions, is qualitatively the same. There is not a summation of diverse functions, but a nonspecialized dynamic function of the tissue as a whole.

"Analysis of the maze habit indicates that its formation involves processes which are characteristic of intelligent behavior. Hence the results for the rat are generalized for cerebral function in intelligence. Data on dementia in man are suggestive of conditions similar to those found after cerebral injury in the rat.

"The mechanisms of integration are to be sought in the dynamic relations among the parts of the nervous system rather than in details of structural differentiation. Suggestions toward a theory of the nature of these forces are presented."

That intelligence is a single dynamic function of the nervous system rather than a summation of diverse functions separately located in the brain is a startling and revolutionary conclusion that will stimulate greatly the work in experimental psychology.

A History of the Medical Department of the United States Army. By P. M. Ashburn, Colonel, Medical Corps, U. S. Army; author of "The Elements of Military Hygiene." With an Introduction by Surgeon-General Merritte W. Ireland. Price, $5. Pp. 448. Cambridge: Houghton Mifflin Company, The Riverside Press, 1929.

The book was written in response to the wish of Surgeon-General Ireland for a somewhat popular account of the growth and achievements of the Army medical department, now under his charge. While writing, the author was librarian of the library of the Surgeon-General's office, now the Army Medical Library, and as such, in ready command of a vast amount of material, which he has used to good advantage, with wise restraint. The book is divided into six parts, covering periods as follows: The first century, 1775 to 1873; up to the Spanish-American War; that war itself; up to the World War; the World War itself; and finally, the period thereafter to 1928. There can be no question as to the accuracy of the presentation, which runs along smoothly and easily and gives the reader a faithful picture of the development of the department in response to emergencies, as well as to the general demand of medical progress. The great achievements of the department through the work of Beaumont, Billings, Reed and other great men are given due consideration and emphasis. Probably pathologists would have enjoyed a fuller account of the Army Medical Museum, its treasures and mode of working. Be that as it may, Ashburn's book gives the story of the War Department in a form that will attract its officers and all who are interested in the development of the kind of service it represents.

Books Received

STERILIZATION FOR HUMAN BETTERMENT. A Summary of Results of 6,000 Operations in California, 1909-1929. By E. S. Gosney, B.S., LL.B., and Paul Popenoe, D.Sc. Price, $2.00. Pp. 194. New York: The Macmillan Company, 1929.

SELECTED READINGS IN PATHOLOGY FROM HIPPOCRATES TO VIRCHOW. Edited by Esmond R. Long, Professor of Pathology, University of Chicago. Price, $4.00. Pp. 301, with 25 plate illustrations. Springfield, Ill.: Charles C. Thomas, 1929.

THE ARMY MEDICAL BULLETIN. Pp. 179. Medical Field Service School, Carlisle Barracks, Penn., 1929.

The Army Medical Bulletin is published from time to time for the dissemination of information relating to administration, preventive medicine, medical field service, and other matters of a medico-military nature. The present number contains a synopsis of the work of the army medical research boards in the Philippines, with abstracts of articles published on the results of this work.

BRAIN MECHANISMS AND INTELLIGENCE. A Quantitative Study of Injuries to the Brain. By K. S. Lashley. Price, $3.00. Pp. 183. Chicago: The University of Chicago Press, 1929.

KLINISCHE EPIKRISEN zugleich beiträge zur Differentialdiagnose. Herausgegeben von Norbert Ortner und Alfred Luger. I. Abdominelle Krankheitzustände. Bearbeitet von L. Berger, J. Blöch, G. Holler, A. Kautzky, V. Kollert, E. Lauda, A. Luger, N. Ortner, K. Paschkis, P. Rezek and E. Silberstern. Price, 8.80 marks. Pp. 151, with 3 illustrations. Vienna: Julius Springer, 1929.

This book consists of ten clinical histories by members of the second medical clinic of the University of Vienna on cases of abdominal disease, supplemented by reports of autopsies. The detailed discussion of clinical manifestations in the light of the revelations post mortem should be illuminating and instructive.

KLINISCHE LABORATORIUMSTECHNIK. Herausgegeben von Prof. Dr. Theodor Brugsch und Prof. Dr. Alfred Schittenheim Zweite, vollständig neu bearbeitete Auflage der "Technik der Speziellen Klinischen Untersuchungsmethoden." IV. Band Unter Mitarbeit von O. Bénesi, K. Birnbaum, H. Elsner, J. Fischer. V. Frühwald, H. C. Jacobäus, F. H. Lewy, W. Meisner, A. Moll, O. Moog, O. Rumpel, H. Runge, J. Schnierer, A. Schwenkenbecher, H. Strauss und W. Wolff. Paper. Price, 50 marks. Pp. 2101 to 2840, with 328 illustrations. Berlin and Vienna: Urban & Schwarzenberg, 1929.

SCIENTIFIC METHOD. Its Function in Research and in Education. By Truman Lee Kelley, Professor of Education and Psychiatry, Stanford University. Cloth. Price, $2.50. Pp. 195. Columbus: Ohio State University Press, 1929.

FELLOWSHIPS AND SCHOLARSHIPS FOR ADVANCED WORK IN SCIENCE AND TECHNOLOGY. Bulletin of the National Research Council no. 72. Second edition. Compiled by Callie Hull and Clarence J. West. Price, $1.50. Pp. 154. Washington, D. C.: The National Research Council, 1929.

REPORT OF THE LABORATORY AND MUSEUM OF COMPARATIVE PATHOLOGY OF THE ZOOLOGICAL SOCIETY OF PHILADELPHIA. By Herbert Fox, M.D., Pathologist. Pp. 65. Philadelphia: 1929.

This report covers the year ending Feb. 28, 1929. It contains interesting notes on animals of special importance, infectious diseases, neoplasms, special subjects of pathologic importance (such as gastric ulcer, leukemia in the monkey and nocardial infection in skunks) and parasites. It is the policy of the institution to place available material at the disposal of scientific workers.

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ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

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ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.40; foreign, $8.75. Single copies, 85 cents.

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